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# Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy: A Case Report and Literature Review

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## Abstract

Hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) is a disorder occurring after hematopoietic stem cell transplant. The disease shares some common features of thrombotic microangiopathy (TMA), a group of disorders with microangiopathic hemolytic anemia, thrombocytopenia and schistocytes. Due to the complex clinical problems in post-transplant patients, accurate recognition and management of TA-TMA are challenging and critical. Here, we report a case of an 18-year-old male with a history of leukemia and stem cell transplant, which was diagnosed with TA-TMA based on clinical and laboratory presentations in the absence of acute renal failure. We discuss and review the major differential diagnoses of TMA, update our understanding of TA-TMA and its diagnostic criteria, and current treatment options of this disorder.

**Keywords:** Thrombotic Microangiopathy (TMA); Hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA); Anemia; Thrombocytopenia; Schistocyte; Acute kidney failure; Infection

## Introduction

Thrombotic microangiopathy (TMA)is a small vascular occlusive disorder, and mainly consists of thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), complement-mediated TMA (atypical HUS), drug-induced TMA and hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) [1]. The common pathophysiology of TMA involves the arteriolar and capillary platelet-mediated thromboses, associated ischemic tissue damage and fragmented red blood cells due to the shear stress across partially obstructed vessels (Figure1). The latter process results in the destruction of red blood cells and hemolytic anemia. Thrombocytopenia mainly results from platelet consumption [2]. Therefore, patients with TMA present such common features as microangiopathic hemolytic anemia, thrombocytopenia and schistocytes in the peripheral blood. However, each disease has its unique characteristics in the etiology, clinical presentation, progression and response to treatment. TA-TMA is one type of TMA disorder, which separates it from other forms of TMA by a unique clinical course and presentation. It occurs in 20-30% of hematopoietic stem cell transplant ationrecipients and usually within 100 days post stem cell transplant [3]. Although it is thought to result from the platelet-mediated thrombosis, it rarely causes kidney functional impairment [1]. The consequence of the disease is severe, with a mortality rate 90-100%, and disseminated fungal infection as a cause of death [1]. Here we present a case of TA-TMA; with its clinical presentations admixed with severe graft versus host disease (GVHD) and sepsis without biopsy confirmation of diagnosis in this critically ill patient, we discuss the disease course, and will focus on the differential diagnoses and diagnostic criteria of TA-TMA and treatment options for this disease.

## Case

An eighteen-year-old male with a history of acute mixed phenotype (T and myeloid) leukemia underwent a double cord blood transplant on June 17. Although he had prophylaxis for graft versus host disease (GVHD) with cyclosporine and mycophenolate mofetil since July, this patient developed skin and grade IV gut GVHD in 2 months. In the meantime, a successful engraftment of the transplanted stem cells was demonstrated by chimeric study. His bone marrow biopsy and smear in October showed increased eosinophils, slightly dysplastic erythroid precursors possibly from chemotherapy treatments but normal counts of white blood cells. Hemoglobin level fluctuated from 8.7 to 10.1 g/dl and platelet ranged from 55 x $10^3$ to 101 x$10^3$/µl. No increased blasts in the bone marrow or peripheral blood smear were observed after the transplantation. On November 15, he was admitted to the pediatric intensive care unit (PICU) for severe abdominal pain, E.coli bacteremia and sepsis. His laboratory

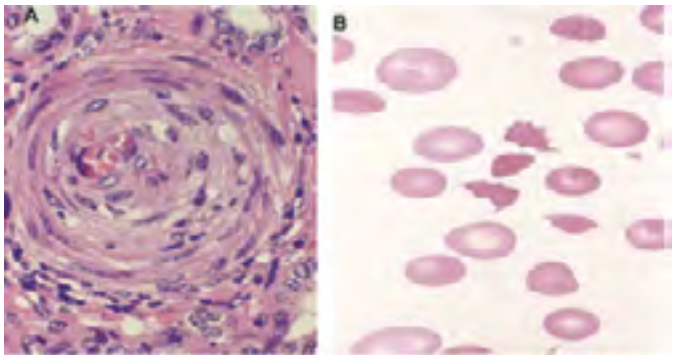


**Figure 1:** Thrombosis and Schistocyte in thrombotic microanggiopathy (TMA)

A: Platelets-mediated thrombosis in small arteries of kidney
B: Fragments of red blood cells (schistocytes) in a smear of peripheral blood

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tests were summarized in (Table 1). He was given intravenous cefepime, flagyl and vancomycin for sepsis. Two days later, his blood culture became negative for any bacterium. On the 6th day of admission, because lab was significant for an elevated LDH, anemia, thrombocytopenia, schistocytes on smear and hypertensive urgency (BP: 175/105 mmHg), thrombotic microangiopathy (TMA) including atypical HUS/TTP/TA-TMA and DIC were suspected. Cyclosporin was discontinued. Serum $C_3$ level (69 mg/dl, reference: 90-180 mg/dl) was decreased, while $C_4$ and $CH_{50}$ were normal. Results of ADAMT $S_{13}$ activity and inhibitor were pending. Atypical HUS was highly suspected. Eculizumab was given and five day treatment did not show improvement in the platelet count and LDH level. Plasma pheresis was initiated when signs of sepsis were resolved. However, results of ADAMT $S_{13}$ showed 65% activity (normal reference: 50-140%) and no inhibitory antibody was detected. In fact, he did not respond to plasma pheresis treatment and his medical conditions deteriorated. His leukocyte count was maintained at or above the lower normal limit, but both platelet and hemoglobin ranged from 7-26 $x10^9$/L and 3.0-10.0 g/dl respectively, and the patient was transfusion-dependent. From December 10, he developed disseminated candidiasis involving multiple organs including the central nervous system, and died of the disseminated fungal infection and gastrointestinal bleeding within two weeks.

## Discussion

The double umbilical cord blood transplantation was successful in this patient and the engraftment was clearly demonstrated in October before his last admission, with 100 % donor cells in chimera check and an absolute neutrophil count being above 5000/μl, platelets being over 80 x $10^9$/L and hemoglobin over 9.0g/dl, before he became transfusion-dependent. While GVHD was present, this patient developed a feature of thrombotic microangiopathy (TMA) since November 21. First, he had microangiopathic hemolytic anemia with hemoglobin dropped to 5.8 g/dl, serum LDH increased to 1272 μ/l, indirect bilirubin increased to 1.4mg/dl, haptoglobin dropped to less than 7 mg/dl. Secondly, he developed thrombocytopenia (platelets count dropped to 12 $x10^9$/L).Thirdly, his peripheral blood smear had a modest presence of schistocytes, which is a characteristic feature of TMA. DAT was negative, which indicated that this is not due to antibody-mediated hemolysis. Finally, he had trilineage hematopoiesis in bone marrow biopsy in October without abnormal population of blasts, indicating he had no morphological evidence of relapsed leukemia. The abnormal hematological findings were consistently shown through the course of his hospital stay. Therefore, it is sufficient for a diagnosis of TMA. However, multiple disorders with distinctive etiology and management including TTP, HUS, a HUS and TA-TMA can show characteristics of TMA (Table 2). It is, therefore, essential to distinguish them and manage the patient accordingly. The differential features of these diseases are summarized in table 2 and discussed below.

## Thrombotic Thrombocytopenic Purpura (TTP)

As shown in table 2, TTP is caused by the decreased activity of A Disintegrin and Metalloproteinase with Thrombospondin Motifs 13 (ADAMT $S_{13}$), a zinc-containing metallo protease that cleaves von Wille brand factor(VWF) to prevent it forming polymers [4]. Reduced activity of ADAMT $S_{13}$ occurs when the gene encoding ADAMT $S_{13}$ is mutated in the familial form or when there are inhibitory auto-antibodies in the acquired form [4-6]. In both situations, $ADAMTS_{13}$ fails to cleave large von Wille brand multimers, thus, leading to the formation of platelet thrombosis in arteriolar and capillaries. Clinically acute renal failure rarely occurs or kidney injury is only minimally present, which can differentiate it from others with acute kidney injuries such as HUS and atypical HUS [1]. The first line treatment of TTP is plasma exchange or plasma pheresis. With this treatment, patients rapidly improve clinically with a complete remission response in 70-80% of patients [7], compared to 90% mortality rate of TTP without treatment. For the acquired form of TTP, given itsauto immune nature, high dose of methyl prednisolone has shown improved out comesin addition to plasma pheresis therapy [8]. Moreover, rutaximab, a monoclonal antibody against $CD_{20}$ that has been used to treat non-Hodgkin's lymphoma, has shown to successfully decrease the relapse risk and prolong relapse-free period in conjunction with plasma pheresis [8-10]. Treatment of rutaximab has become the frontline therapy for TTP. In this patient, the laboratory tests howed consistently normal creatinine

| | Results (11/15) | Results (11/21) | Reference Interval |
|---|---|---|---|
| White Blood Cell | 20,000 | 6200 | 4.5-11.0 x103/μl |
| Hemoglobin | 10.7 | 5.8 | 11.7-15.0 g/dl |
| Hematocrit | 24% | 18.5 | 34.0-47.0 g/dl |
| Platelet | 24 x 103 | 12x 103 | 150-450 x103/μl |
| PT | 15.7 | 13.2 | 12.3 – 14.9 seconds |
| PTT | 33 | 32 | 25.4 – 34.9 seconds |
| D-dimer | 0.69 | 10.64 | < 0.5 μg/ml |
| Fibrinogen | 225 | 368 | 175-450 mg/dl |
| LDH | 369 | 1272 | 100-220 μ/L |
| Bilirubin total | 0.8 | 2.1 (Bil-direct: 0.7) | 0.1-1.2 mg/ml |
| BUN | 19 | 52 | 11-25 mg/dl |
| Creatinine | 0.79 | 1.04 | 0.4 – 1.2 mg/dl |
| Haptoglobin | < 7 | < 7 | 30-200 mg/dl |
| Schistocytes | None | Modest | None |
| Direct anti globulin test | Negative | Negative | Negative |
| Urinalysis | Negative | Protein 100 mg/dl | Negative |
| Blood pressure | 125/82 | 175/105 mmHg | 140/90 mmHg |

**Table 1:** The laboratory findings on November 15 and 21 of the patient

| | Pathophysiological etiology | Distinctive clinical features | First line treatment |
|---|---|---|---|
| TTP (Thrombotic thrombocytopenic purpura) | Decreased ADAMTS13 activity due to genetic alterations to the gene or presence of inhibitory autoantibodies | 1) No or mild acute kidney injury<br>2) Reduced ADAMTS13 activity <10%; or presence of autoantibodies<br>3) Response to plasmapheresis | Plasmapheresis with fresh frozen plasma and Rituximab +/- steroid |
| HUS (Hemolytic uremic syndrome) | 1) Shiga toxin-producing E. coli or S. Pneumoniae<br>2) Cobalamin C or diacylglucerol kinase ε deficiency<br>3) Complication of drug, solid organ transplant or infection | 1) Following gastroenteritisand bloody diarrhea or. Pneumoniaesepsis in a pulmonary infection<br>2) Acute kidney injury | Antibiotics and Supportive |
| aHUS (atypical hemolytic uremic syndrome) | Abnormal activation of alternative complement system due to<br>1) Genetic mutations in complement factors<br>2) Inhibitory autoantibodies to factor H and I | 1) Following acute respiratory infection or gastroenteritis<br>2) Acute kidney injury<br>3) Thrombocytopenia is mild or absent in 15-20% patients | Eculizumab |
| DIC (disseminated intravascular coagulation) | Over-activation of coagulation pathway | 1) Bleeding and blood oozing<br>2) Prolonged PT and PTT<br>3) Decreased fibrinogen | 1) Treat the underlying disease<br>2) Platelet and coagulation factors for severe bleeding patients |
| TA-TMA (hematopoietic stem cell transplant-associated thrombotic microangiopathy) | Unknown | 1) Post hematopoietic stem cell transplantation<br>2) Without or with mild acute kidney injury<br>3) Often with disseminated fungal infection | 1) No response to plasmapheresis<br>2) Eculizumab if serum $C_5b$ is elevated<br>3) Clinical trials on going |

**Table 2:** Etiology, clinical features and treatment in major disorders with thrombotic microangiopathy (TMA) (anemia, thrombocytopenia and schistocyte)

and mildly increased BUN during the entire course. Among the common types of TMA, TTP rarely cause acute kidney injury, therefore TTP should be the first one to consider. However, several lines of evidence did not support this patient had TTP. First, repeat procedures of plasma pheresis did not improve the condition of this patient. His platelets remained low (<20 x $10^9$/L) and LDH remained high. Secondly, the measured activity of ADAMT $S_{13}$was found to be 65% of the normal activity (normal reference: 50% - 140%). This result implies that the function of ADAMT $S_{13}$ in this patient is at the normal level. Finally, no inhibitory auto antibodies in the patient were detected, suggesting he did not suffer from an idiopathic TTP. Therefore, we excluded the possibility of TTP.

## Hemolytic Uremic Syndrome (HUS) and Atypical HUS

Hemolytic-uremic syndrome (HUS) consists of a group of heterogeneous disorders including infection-induced HUS, Cobalamin C defect HUS and HUS with coexisting disease such as malignancy, solid organ transplant, malignant hypertension and autoimmune disease [11]. The infection-induced HUS are mostly common (85-90%) and usually occurs a week after an episode of preceding bloody diarrhea caused by *E. coli* O157: H7 [12]. Infection with the *E. coli* serotypes, *Shigella dysenteriae* and *S. Pneumococci* can also cause HUS in children and adults [12]. These pathogens produce Shiga toxin, which binds to globotriaosylceramide (Gb3) and globotetraosylceramide (Gb4) of the endothelial cells, renal mesangial cells and podocytes [13,14]. The consequence is induction of damage and apoptosis [15].The clinical presentations of HUS are TMA with acute renal failure. Acute kidney injury is shown with rapidly rising serum creatinine level [16] in up to 55-75% of patients, and some even need dialysis [17]. Approximately 25% of HUS patient will develop chronic renal insufficiency [14] and 10-20% have neurological involvement (stroke, seizure) [14].Treatment of HUS is mainly supportive and early administration of antibiotics [11]. Plasma infusion or plasma exchange is controversial in the effectiveness of treatment [11]. Atypical HUS (aHUS) is mediated by excessive complement activation. It is not associated with infection by shiga-toxin-producing *E-coli* [12], but with dysregulation of the alternative compliment pathway. Mutations in genes encoding multiple compliment regulatory proteins, including complement factor H (CFH)[18,19], membrane cofactor protein (MCP) [20], complement factor I (CFI) [21], factor B [22]and factor $C_3$ [23]causes the familial type of this disease. Autoantibodies in human serum against factors H and I cause acquired atypical HUS [24,25]. Factor H deficiency or dysfunction is the prototype of aHUS. The auto-antibodies prevent factors from binding to the ligands such as $C_3b$, $C_3b$ and $C_3d$ [26]. As a consequence, the normal complement factor function is impaired, leading to over-activation of the pathway and tissue damage [27]. The clinical presentation is nonspecific. Half of the patients may develop oliguria or anuria and need dialysis [28]. The treatment of aHUS used to be plasmapheresis, but no evidence suggests the effectiveness of this procedure for aHUS [11]. An Italian cohort study indicated that plasmapheres is provides a complete hematological remission in 78% of children and 53% of adults, but half of children and two third of the adults developed an end stage renal failure or died within 3 years of follow-up [29]. This suggested the ineffectiveness of plasmapheresis. Eculizumab revolutionized the treatment of aHUS. It is a

recombinant monoclonal antibody targeting the complement $C_5$. It inhibits the normal function of $C_5$ and prevents its cleavage and activation of terminal complement pathway. Clinical studies suggested that eculizumab treatment achieved event-free status in 84% of aHUS patients and a normalization of hematology and increase GFR in 90% of patients during 2 years of follow-up [11,30]. For the case we present here, he had no signs of acute renal failure or chronic renal insufficiency throughout the course. His serum creatinine and BUN levels remained close to the normal and he did not have oliguria or anuria during the entire course of hospitalization. Although complement $C_3$ was low, that could be due to the bacterial infection. In particular, he received several days of eculizumab treatment, but there was no improvement. Due to GVHD, he had an *E-coli* bacteremia but it was not involved in *E-coli* O157: H7 strain or any strains that produce shiga-like toxin. Together, we could exclude the possibility of HUS or atypical HUS.

## Disseminated Intravascular Coagulation (DIC)

DIC often develops in the setting of bacteremia, trauma, cancer or obstetric complications or massive tissue injury. It is not a part of TMA but has similar clinical manifestations of TMA with microangiopathic hemolytic anemia, schistocyte and thrombocytopenia. The underlying mechanism of DIC is different from TMA. DIC is due to over activation of coagulation pathways in both intrinsic and extrinsic pathways [31]. Therefore, the development of DIC will accompany the consumption of coagulation factors and fibrinogen. Due to the formation of fibrin and its cleavage the D-dimer is dramatically elevated. As a result of a significant reduction in coagulation factors, there are significantly increased PT and PTT [31]. In the patient we described here, he had bacteremia and might have inflammatory damages to the tissue, but his PT/INR, PTT and fibrinogen level were consistently within normal limits. The D-dimer was slightly elevated during the course, which could result from the breakdown of the thrombosis. Therefore, we excluded the possibility of DIC in this patient.

## Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy (TA-TMA)

Similar to the diseases discussed above, TA-TMA is also caused by the platelet mediated vascular thrombosis [32, 33]. It usually presents as anemia, thrombocytopenia, pulmonary hypertension, gastrointestinal symptoms, central nervous system injury and renal impairments [34]. Because of complicated clinical presentations in these patients, the diagnosis of TA-TMA is obscured by multiple other post-transplant complications such as infections, graft-versus-host disease (GVHD) or failed bone marrow engraftment. Because of this, the disease was not initially recognized as a separate entity, and instead was treated with plasma exchange as TTP [35, 36]. But, these patients usually have a nearly normal range of ADAMT $S_{13}$ activity and did not respond to treatment of plasma exchange. Eventually they frequently die of disseminated bacterial or fungal infections [35]. Since the early1980s, however, some of these patients have been found to have small vessel thrombosis in kidneys and developed acute renal failure [34, 37], with features similar to those of atypical HUS with complement activation. Risks factors for development of TA-TMA are diverse. Although many think that GVHD might increase the risk of TA-TMA, a recent cohort study showed that GVHD itself does not confer an elevated risk of TA-TMA development [38]. However, the prophylactic medications of GVHD such as cyclosporine and tacrolimus have been well established as a strong risk factor for TA-TMA since the earliest reports [35,37,39]. Well-known risk factors also include advanced age, female sex and preconditioning radiation therapy [36,40,41]. The diagnosis of the TA-TAM is based on the histology of organ biopsy or the clinical presentations whenever biopsy is not feasible in these severely ill patients. The histological features are those of vascular damages such as thickened capillary walls, occluded vascular lumens, fibrin deposition or necrosis [42, 43]. However, in patients without biopsy like the case presented here, laboratory markers are the determining factors for diagnosis [2, 44]. They are elevated LDH, proteinuria >30mg/dl or random urine protein/random urine creatinine ratio ≥2 mg/dl, hypertension, thrombocytopenia, anemia and schistocytes in the peripheral blood. In detail, when elevated LDH, proteinuria and hypertension are present, a diagnosis of TA-TMA can be considered. When schistocytes, thrombocytopenia and anemia co-exist, the diagnosis of TA-TMA can be made [33,43].The presence of proteinuria and activation of terminal complement $C_5$b-9 indicates a poor prognosis [43]. Patients who have both proteinuria and activation of $C_5$b-9 have a significantly decreased 50% survival rate (around 100 days post transplantation) comparing with those who do not have them [43]. Additional version of diagnostic criteria of TA-TMA is used by four groups and summarized recently by O but et al. [45]. TA-TMA is diagnosed based on increased LDH, decreased platelet (<50 x $10^9$/L or <50% of normal baseline), schistocytes (present or >2/hpf), decreased haptoglobin and negative DAT. This version of diagnosis has less concern on the kidney injury.

The patient described here had no biopsy, but presented with features of TMA on November 21, which included thrombocytopenia, anemia and modest schistocytes in the peripheral blood. In addition, he had elevated LDH (1272 μ/l), hypertension (175/105 mmHg), and proteinuria (100mg/dl), which is consistent with the diagnostic criteria of TA-TMA [43], while other differential diagnoses are excluded as described above. In addition, it meets the diagnostic criteria presented by four groups [45] (Table 1).The fungal infection developed in the later stage of disease. It is not the cause of disease, but it may further damage the endothelial cells of blood vessels and contribute the severity of disease and mortality. Treatment of TA-TMA is challenging. Plasma pheresis does not provide benefits to these patients. If both proteinuria and elevated serum $C_5$b are present, treatment with eculizumab, an antibody targeting complement $C_5$ cleavage, might be given [46].This is because dysregulation of complement factors has been found in some TA-TMA patients [44]. Recent clinical investigations with eculizumab treatment show a significant increased survival rate (62% of 1 year survival rate in treatment groups versus 9% of rate in non-treatment group following TA-TMA diagnosis, p=0.0007) [46-48]. A prospective cohort study is currently undergoing to investigate the effect of eculizmab in treatment of TA-TMA comparing with those with stem cell transplants but no diagnosis of TA-TMA (NCT02604420). A different clinical trial to test OMS721 in the treatment of TMA including TA-TMA is currently in phase II clinical trial. OMS721 is a monoclonal antibody raised to specifically target MASP2 to prevent activation of complement system (NCT02222545). For patients without proteinuria or serum $C_5$b increase, supportive treatment is utilized only. If calcineur in inhibitors such as cyclosporine, tacrolimus or sirolimusare used for GVHD prophylaxis, the usage of them are found to associate with an increased risk of TA-TMA [39]. Therefore, calcineurin inhibitors need to be reduced or withdrawn to treat TA-TMA. Studies found that withdrawal of them provides 50-60% response [38].A recent report in a retrospective study showed that recombinant human soluble thrombomodulin (rTM) significantly increased the overall survival of TA-TMA that is associated with prophylactic use of calcineurin inhibitors [47]. Multiple individual reports on treatment of TA-TMA have shown good responses to rituximab [48,49], defibrotide [50], vincristine [51] and pravastin [52]. In line with rituximab's success in treatment of TTP, the response rate of TA-TMA to rituximab is about 80% in some reports, and with longer survival benefits. The mechanism of action is unknown for rituximab. Unfortunately, rituximab was not tried in our patient. Sixty seven percent response rate for defibrotide; 50% - 86% response rate for vincristine with a longer survival benefit [52]. For all reports, the numbers of cases are not large enough and the effect of these agents has not been confirmed by randomized, double blind clinical trials in multiple medical centers.

## Conclusion

TA-TMA is a fatal disease following hematopoietic stem cell transplantation. It is very important to differentiate it from other disorders which shares clinical presentations of TMA (Figure 2). Anemia, thrombocytopenia and schistocytes are the baseline presentation of the disease, while the absence of kidney injury, increase LDH, proteinuria and hypertension are diagnostic for HA-TMA if an organ biopsy is not available. The disease is still largely fatal and new treatments are not available and new medications are under clinical trial investigation.

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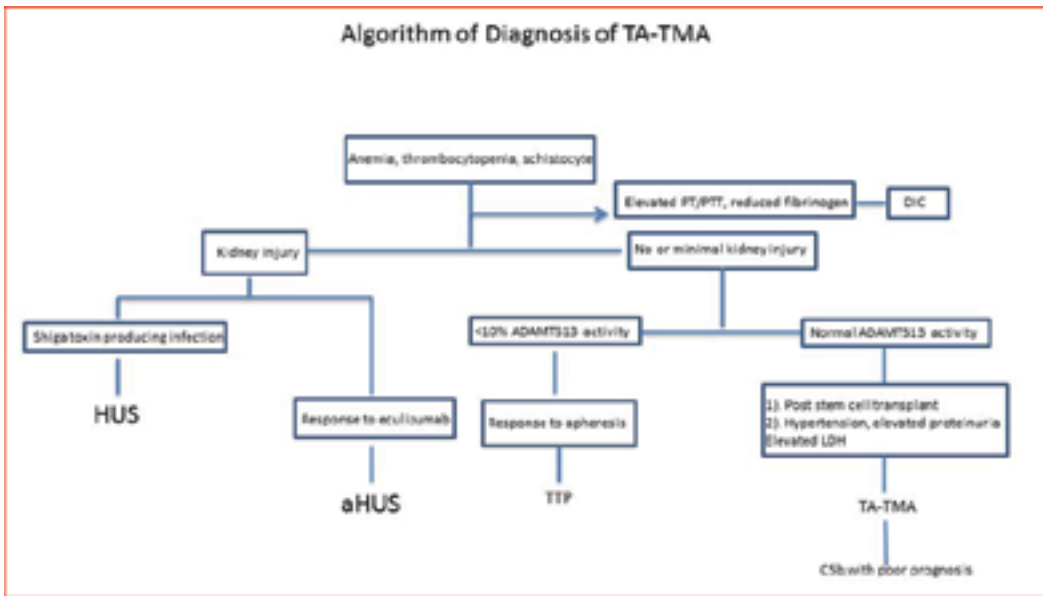


**Figure 2:** algorithm for diagnosis of TA-TMA, HUS, aHUS, TTP and DIC, based on the laboratory tests and major clinical signs

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