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Case Report

Causal ambiguity: deciphering the etiology of secondary thrombotic microangiopathy with systemic lupus erythematosus and vivax malaria

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ABSTRACT

Hemolytic uremic syndrome (HUS) falls under the spectrum of thrombotic microangiopathy (TMA) characterized by microangiopathic hemolytic anemia, thrombocytopenia, and thrombi in small vessels leading to end-organ damage. It's classified into typical HUS (caused by Shiga toxin-producing *E. coli*), atypical HUS (due to uncontrolled complement activation), and secondary HUS (sHUS) linked with coexisting conditions. We present a compelling case of a 21-year-old female with fever, jaundice, anemia, thrombocytopenia, and oliguric acute kidney injury (AKI), ultimately diagnosed with Plasmodium vivax malaria. Despite adequate antimalarial therapy, the patient's clinical trajectory remained intricate, characterized by sustained hematological abnormalities and renal dysfunction. A comprehensive assessment revealed Coombs-negative hemolytic anemia. Subsequently, a renal biopsy confirmed TMA. Considering the rarity of vivax malaria causing TMA, an autoimmune workup was conducted, suggesting systemic lupus erythematosus (SLE). Systemic autoimmune disease-associated HUS (SAID-HUS) is a rare entity that exhibits diverse clinical presentations, with SLE being best-described etiology in literature. SLE-associated HUS was considered and was managed with steroids and hydroxychloroquine resulting in significant renal and hematological improvement. This report underscores significance of assessing autoimmune factors in case of secondary TMA, while also shedding light on evolving understanding of vivax malaria's potential relationship with TMA.

Keywords: HUS, TMA, Secondary HUS (sHUS), SLE, SAID-HUS, Plasmodium vivax malaria

INTRODUCTION

TMA encompasses several clinical entities, including thrombotic thrombocytopenic purpura, HUS, and complement-mediated TMA. This latter group includes atypical HUS (aHUS) and sHUS. aHUS due to the deregulation of the alternative complement pathway. Of note, when TMA is associated with an underlying condition such as infections, autoimmune disorders, or malignancy, it is referred to as sHUS.[1]

In this report, we present a case illustrating the intricate interplay of secondary TMA with SLE and vivax malaria. The challenges in determining the etiological basis of TMA, the diagnostic considerations, and the therapeutic decisions are discussed within the context of this complex clinical scenario.

CASE REPORT

A 21-year-old female presented with a one-week history of high-grade intermittent fever with chills. Her initial symptoms were followed by yellowish discoloration of the eyes and high-colored urine, which progressed to a gradual reduction in urine output over the subsequent four days. Upon examination, she had notable pallor, icterus, facial puffiness, and pedal edema. Her vital signs at admission included a febrile state with an axillary temp

of 100.8°F, pulse rate of 98/min, blood pressure of 112/70 mm Hg, and room air oxygen saturation of 94%. Systemic examination revealed bilateral infra-scapular coarse crepitations and liver span of 17 cm.

Her initial evaluation revealed anemia, thrombocytopenia, oliguric acute kidney injury, and hyperbilirubinemia with transaminitis (Table 1). Abdominal ultrasonography showed enlarged liver measuring 17.8 cm and normal spleen size. Both kidneys showed increased cortical echogenicity with a mixed streak of perinephric fluid and bilateral pleural effusion. 2D ECHO showed trace pericardial effusion.

A comprehensive diagnostic workup led to a diagnosis of Vivax malaria based on a positive vivax malaria antigen test and the presence of Plasmodium vivax trophozoites on a peripheral smear. Investigations for other potential tropical infections and viral hepatitis yielded negative results (Table 1). Glucose-6-phosphate dehydrogenase activity was within the normal range. Guided by national treatment guidelines, she received intravenous artesunate and oral primaquine therapy. Hemodialysis was instituted on alternate days, accompanied by transfusions of packed red blood cells and single donor platelets to manage anemia and thrombocytopenia, respectively.

As her fever gradually subsided and liver function improved, her clinical status remained complicated by ongoing oliguria, hemodialysis dependence, worsening creatinine levels, and persistent thrombocytopenia and anemia. Urine analysis indicated trace proteinuria and microscopic hematuria. Peripheral smear examination revealed fragmented red blood cells. Further assessment for hemolysis revealed elevated lactate dehydrogenase levels (3864 IU/L), negative direct and indirect Coombs tests, low C3 levels (604 mg/l), and normal C4 levels (130 mg/dl), suggestive of alternate pathway activation. Furthermore, anti-nuclear antibody (ANA) immunofluorescence demonstrated positivity at a titer of 1:100, displaying a 3+ speckled pattern. Anti-PCNA (Proliferating cell nuclear antigen) antibodies were found to be 3+ positive, a finding associated with 1% of SLE cases. Anti-proteinase-3 and anti-myeloperoxidase antibodies were negative. lupus anticoagulant, IgM and IgG anticardiolipin antibodies were negative.

Subsequently, her renal function further deteriorated, culminating in peak creatinine level of 8.9 mg/dl by tenth day. Later, kidney biopsy was performed, revealing presence of TMA characterized by patchy cortical necrosis (Figure 1). Steroids and hydroxychloroquine were initiated, resulting in significant renal and hematological improvement.

Upon discharge, patient exhibited improved hemoglobin levels (9 g/dl), platelet count (549,000/µl), and serum creatinine (3.17 mg/dl). Subsequent mycophenolate mofetil therapy led to sustained renal recovery, with serum creatinine level of 1.3 mg/dl after 2 months.

Table 1: Baseline investigations of patient in our hospital.

Test	Result
Hemoglobin	8 gm/dl
Total leucocyte count	5.21 thous/microliter
Platelet count	13 thous/microliter
Creatinine	5.89 mg/dl
Sodium	132 mEq/l
Potassium	4.03 mEq/l
Total protein	5.04 mg/dl
Serum albumin	2.37 mg/dl
Total bilirubin	6.5 mg/dl
Direct bilirubin	5.01 mg/dl
AST	204 IU/l
ALT	307 IU/l
ALP	290 IU/l
GGT	98 IU/l
CRP	51 mg/dl
Procalcitonin	124 ng/dl
Ferritin	897 ng/ml
HIV serology	Negative
HCV/HbsAg/HAV/HEV serology	Negative
Dengue NS1/IgM	Negative
Leptospira IgM	Negative
Scrub typhus IgM	Negative

Abbreviations: AST-Aspartate aminotransferase, ALT-Alanine aminotransferase, GGT-Gamma-glutamyl transferase, ALP-alkaline phosphatase, ESR-Erythrocyte sedimentation rate, CRP-C-reactive protein, HIV-Human immunodeficiency virus, HCV-Hepatitis C virus, HbsAg-Hepatitis B surface antigen, HAV-Hepatitis A virus, HEV-Hepatitis E virus.

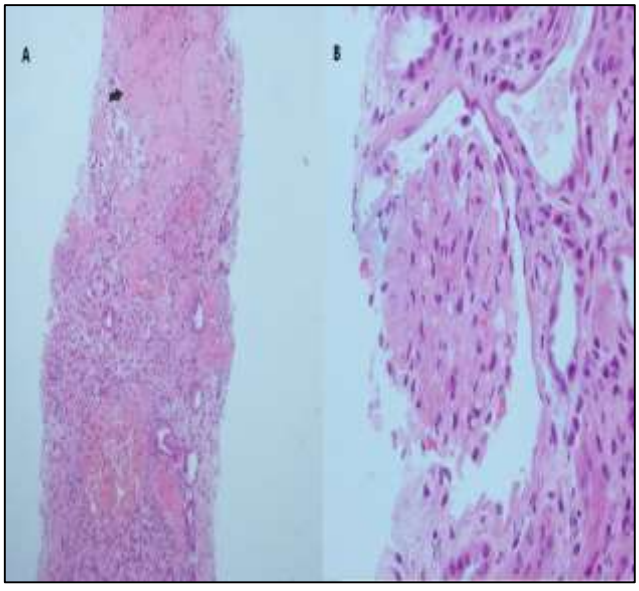

Figure 1: (A) Kidney biopsy photomicrograph showing ischemic necrosis with ghost outline of tubules (arrow) and fibrinoid necrosis in blood vessels (H and E, 200x); and (B) Congested glomeruli, fibrillary appearance of mesangium with endothelial cell swelling and microthrombi (H and E, 400x).

DISCUSSION

TMA is characterized by the development of microvascular thrombosis within arterioles and capillaries. The pathogenesis involves a triggering event that leads to excessive activation of the alternative complement pathway, leading to the formation of a membrane attack complex. Consequently, this complex induces endothelial damage, setting off the coagulation cascade and establishing a prothrombotic state.[2] Clinically, this manifests as Coombs-negative hemolytic anemia, thrombocytopenia, and significant end-organ damage, with the kidneys being frequently affected.[3]

TMA encompasses several clinical entities, including TTP, HUS, and complement-mediated TMA. This latter group includes aHUS, attributed to genetic mutations in the complement pathway, and sHUS. The etiology of sHUS involves various conditions such as infections, autoimmune disorders, and malignancy.[3]

The genetic mutations are mainly identified in patients with childhood-onset, recurrent, and/or familial HUS.[3] Further, the screening for complement mutations is not widely available. Our patient did not undergo genetic testing for complement mutations considering she had a known underlying autoimmune and infectious trigger for the TMA (SLE and/or P. vivax Malaria). Furthermore, she did not have childhood-onset or familial history of TMA. The absence of preceding diarrhea and low complement level which responded to immunosuppressive therapy suggested that TMA was not secondary to infection with a Shiga toxin-producing organism or an inherited disorder of the complement pathway.

In our patient, a diagnosis of sHUS was made. The triggering event, Vivax malaria, or SLE is certainly hard to comment upon, however, in our case, the worsening of the patient even after adequate antimalarial treatment and sustained response to immunosuppression favors SAID-HUS.

SAID-HUS is a rare disorder within the spectrum of TMA. It has a diverse presentation with SLE being the best-described etiology in the available literature.[4-6] In the context of SLE, a study on lupus nephritis revealed a higher prevalence of renal TMA secondary to SLE (24.3%) compared to previous reports (0.5% to 10%), indicating potential underdiagnosis due to overlapping presentations.[4] It is known as one of the most severe forms of renal vascular disease in SLE with a high mortality rate and appears to be an independent risk factor for renal outcome in lupus nephritis.[4] A registry encompassing 60 patients with SLE-associated TMA, revealed triggering factors including lupus flares, infections, pregnancy, and medication non-compliance.[7] In a case series, two out of seven patients were diagnosed with SLE upon presentation with TMA as in our case, while for others, the duration of primary disease prior to the onset of TMA varied from three months to eleven years.[3]

The therapeutic strategy for SAID-HUS lacks a definitive consensus. Typically, treating the underlying SAID with immunosuppressive agents has shown promising results in managing both the TMA and its associated SAID.[8] Despite limited evidence for its effectiveness in SLE and other connective tissue disorders, therapeutic plasma exchange has been utilized, especially in refractory cases.[9] A systemic review has similarly not substantiated the efficacy of eculizumab in SLE-associated TMA.[10]

AKI is not commonly associated with Vivax malaria and when it occurs, it is often attributed to mixed undiagnosed falciparum infection or coexisting factors such as sepsis, dehydration, or hypotension. Complicated malaria can mimic TMA. While malaria isn't confirmed to cause TMA, evidence suggests a connection.[11,12] Bhadauria et al found 4 cases of TMA in P. vivax malaria out of 251 AKI cases.[11] Sinha, et al reported 9 TMA cases linked to P. vivax.[12] High suspicion is key for TMA diagnosis in malarial AKI, especially with ongoing anemia, low platelets, and non-recovering renal failure, as these patients may improve with therapeutic interventions like plasmapheresis. The relationship between vivax malaria and TMA remains somewhat ambiguous, leaving open the question of whether this connection is causative or simply a matter of coincidence.

CONCLUSION

This case report highlights the intricate interplay of secondary TMA in the context of SLE and vivax malaria. SAID-HUS is difficult to diagnose due to knowledge gaps that range from etiology to clinical presentation, and treatment strategies. This report emphasizes the importance of considering autoimmune factors in cases of secondary TMA and highlights the evolving understanding of vivax malaria's potential relationship with TMA.

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