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A Rare Case of Tuberculosis Associated Thrombotic Microangiopathy with Diagnostic Challenges

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Running Title: *Thrombotic microangiopathy in tuberculosis.*

Abstract: ***Thrombotic microangiopathy (TMA) is a clinicopathological entity characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction, particularly renal involvement. While commonly associated with Shiga toxin, complement dysregulation, malignancy, or drugs, tuberculosis-associated TMA is exceedingly rare and diagnostically challenging. We report the case of a 13-year-old female who presented with intermittent fever with chills for 20 days, diffuse abdominal pain for 15 days, and features of intestinal obstruction for 3–4 days, along with decreased urine output for 2 days. There was no history of weight loss, altered appetite, gastrointestinal or urinary bleeding, altered sensorium, long-term medication use, or past tuberculosis exposure. On examination, she was febrile (100.4 °F), hemodynamically stable, with pallor and bilateral pedal edema. Abdominal examination revealed right iliac fossa tenderness, distension, and sluggish bowel sounds. Laboratory evaluation showed neutrophilic leukocytosis, macrocytic anemia (Hb 6.7 g/dL, MCV 105), thrombocytopenia (25, 000/µL), indirect hyperbilirubinemia, elevated LDH (>1000 IU/L), uric acid 9.3 mg/dL, and renal dysfunction (urea 131 mg/dL, creatinine 4.9 mg/dL). Urinalysis revealed 2+ proteinuria with 1.5 g/day proteinuria and 10–20 pus cells/hpf. Imaging and ascitic fluid findings, along with a positive TST (25 mm), supported a diagnosis of abdominal tuberculosis, and anti-tubercular therapy (ATT) was initiated. Autoimmune, viral, and parasitic workups were negative. Renal biopsy was deferred initially. One-month post-discharge, she had recurrent anemia, worsening renal function, and increased proteinuria (2.9 g/day). Schistocytes (>10/hpf) were identified, and renal biopsy confirmed TMA. She was treated with plasma exchange alongside ATT. This case highlights tuberculosis as a rare but significant secondary cause of TMA. Early suspicion and renal biopsy in deteriorating patients are vital for diagnosis and management.***

Keywords: Thrombotic microangiopathy (TMA), Tuberculosis related TMA, Hematological disorders, Infection induced TMA, Diagnostic challenges in TMA.

1. Introduction

Thrombotic microangiopathy (TMA) is a vaso-occlusive disorder affecting the small vessels with microthrombi within the vessel lumen causing intravascular hemolysis, leading to microangiopathic hemolytic anaemia and thrombocytopenia. Multiple organ involvement can be seen in TMAs, more commonly affecting renal & neurological system involvement. TMA commonly are due to infection related, complement mediated, metabolism associated or drug induced. Clinical conditions that also presents as TMA are HELLP syndrome, Sepsis & DIC, autoimmune disorders like lupus, systemic sclerosis, catastrophic APS; malignancy, malignant hypertension, post transplantation.[1]

Infection associated TMA is most commonly caused by E157; O7 shiga like toxin (STEC-HUS; 80–90 % of the cases) followed by shiga toxin of shigella and streptococcus pneumoniae [2].

Tuberculosis (TB) has been associated with multiple hematological alterations such as monocytosis, leukocytosis, anaemia, pancytopenia as well as autoimmune phenomena such as granulomatosis with polyangiitis and systemic lupus erythematosus. The association between thrombotic thrombocytopenic purpura (TTP) or TMA and tuberculosis

are extremely rare, with very few cases reported in the literature.[3]

Here we are presenting a case of young Indian female who presented with thrombotic microangiopathy secondary to infection likely tuberculosis as causal association and the possible caveats in reaching a diagnostic accuracy.

2. Case Report

Our patient is a case of 13 years old female, resident of Delhi, presented with complaint of intermittent fever of 100-102 °F, with chills for 20 days; diffuse dull pain in abdomen with no particular site of radiation or referred pain for 15 days along with non-passage of flatus and faeces and Abdominal distension for 3-4 days with non-projectile vomiting and decrease in Urine Output for 2 days, she denied any history of cough, sore throat, shortness of breath, chest pain, palpitations, diarrhoea, burning micturition, gross hematuria, any focal neurological deficit, altered sensorium, abnormal body movement, history of any long term drug intake; any similar history in past or any history of tuberculosis or tuberculosis exposure in the past, history of weight loss, any swelling, decrease appetite, melena, blood in stools. On general physical examination, the patient was conscious, oriented to time, place & person & hemodynamically stable with fever documented at 100.4°F with pallor and pedal edema; Cyanosis/Clubbing/Lymphadenopathy was absent. On per abdominal examination, generalised distension of abdomen with tenderness was present over right iliac fossa. Bowel sound was sluggish in all quadrants of abdomen; no hepatosplenomegaly was palpable no shifting dullness was appreciable. No focal neurological deficits were present on CNS examination. Respiratory Examination & Cardiovascular examination were within normal limit. Her qualitative urine test for HCG was negative. Her initial investigations are depicted in table 1.

Table 1: Initial lab parameters of our patient

Parameters		**On Presentation**
Haemoglobin (gm/dl)		6.7 (MCV: 105)
Total leukocyte count (per µL)		21700/ µL (81% polymorphonuclear)
Platelet Count (per µL)		25, 000/ µL
Haematocrit		29.7
ESR		**110 mm in 1st hour**
PS for Schistocyte (two reports)		Both reports showed **no** schistocytes.
Na+/ K+ (meq/L)		127/ 4.4
Urea/ Creatinine (mg/dl)		131/ 4.9
Total Bilirubin/Indirect Bilirubin **(mg/dl)**		**3.9/2.96**
AST/ALT/ALP (IU/L)		45/20/123
Total Protein/ Serum Albumin (gm/dl)		5.5/ 2.5
Calcium/ Phosphate in mg/dl		6.3/ 4.1
LDH in IU/L & UA in mg/dl		**> 1000/ 9.3**
PT/ INR/**D dimer**		17.1/ 1.26/**3098**
Total Cholesterol/Triglyceride/HDL/LDL (mg/dl)		187/358/28/69.39
Procalcitonin		7.90 (raised)
S amylase/ S lipase (IU/L)		33/44
S. Iron/ S. Ferritin/ S. Folate/ TIBC/ S. Vit B12		40/1203/10/247/160 (pg/ml)
T3/T4/TSH		1.5pmol/L (normal); 6.25pmol/L (normal); 1.10µIU/ mL (normal)
Hep A/ Hep E/anti HCV/ HIV/HBsAg/HIV I, II		Negative
PSMP/NS1AG/TYPHI DOT		Negative
ICT/DCT		Negative
Abdominal Xray		Dilated bowel loops were seen; 5-6 air fluid levels were present; no gas under diaphragm seen
CXRAY		B/L lung fields clear; B/L CP angle clear; No cardiomegaly
URM		Ph: acidic; s/p; nil/2+; 10-20 pus cells; 2-3 RBCs/hpf
24 hr U. Protein		1.5gm/day
Urine for active sediment	PH	Ph 6.5
	Protein	2+ Proteinuria
	Sugar	nil
	RBC	3–5/ hpf (fresh) (no dysmorphic RBCs seen)
	WBC	8 – 10 (in clump) / hpf
	Casts/ Crystals	Nil
		Impression: Inactive sediment with moderate proteinuria with non-glomerular haematuria and pyuria.
Urine AFB		Negative
ANA/ANCA/APLA		Negative
C3		78 (normal)
C4		17.5 (normal)
Ascitic fluid		Cells–300 cells (85% lymphocytic, rest polymorphonuclear) Sugar/ protein: 123/ 3.5; SAAG: 0.45; ADA: 87U/L
CA 125 (U/mL)		175 (Increased)
CA19-9/CEA/alpha feto protein /beta HCG		Normal
Tuberculin skin test		25mm (positive)

Her ultrasound whole abdomen report showed Circumferential mural thickening of the cecum; ileocecal junction and the terminal ileum with luminal attenuation of visualised terminal ileum; multiple mesenteric necrotic lymph node; largest measuring 8.5mm in SAD with mild ascites with features suggestive of infective etiology probably TB.

Her Right Kidney & Left Kidney size were 9.7 × 5.1 cm, raised cortical echogenicity was seen with intact corticomedullary junction.

A Provisional diagnosis was made as a case of ileocecal tuberculosis; presented with subacute intestinal obstruction; with sepsis & Acute Kidney Injury (probably sepsis induced or Hypovolemia associated) with bicytopenia & vit B12 deficiency was made. Treatment was started as per protocol. Weight based renal modified anti tubercular therapy (ATT) was initiated. Patient was hemodynamically stable during the course of hospital stay; she improved gradually with improving urine output; kidney function test (KFT). Contrast enhanced CT Abdomen was planned once the KFT becomes normal.

In view of initial evidence of hemolysis, proteinuria & deranged KFT, kidney biopsy had also been planned, but the patient was not willing as she was improving and was discharged on patient's request with ATT and vitamin B12 supplementation at discharge and she was asked to follow up in outpatient department (OPD) with KFT, complete blood count, urine routine and microscopy and 24hr urinary protein. On discharge, patient's Blood Urea was 56 mg/dl; S. cr 1.3mg/dl; her Haemoglobin improved till 11.6gm/dl and platelet count were improved till 2.64 lac/µL, total bilirubin was also settled till 1.2mg/dl. On a follow up visit in OPD after 1 month, she clinically had no fresh complains but her lab parameters worsened with evidence of increased proteinuria of 2.9gm/day with 4-5 pus cells/hpf & 40-50 RBCs/ hpf. She developed anaemia and thrombocytopenia again with haemoglobin 6.7gm/dl & platelet count 71000/ µL on presentation; her serum creatinine value was increased to 3.1mg/dl and urea was 41mg/dl. Total bilirubin was 2 mg/dl and more than 85% was indirect fraction bilirubin and she was admitted again. During this second admission period her repeat ultrasound whole abdomen did not show any mass in right iliac fossa or any inflammatory bowel wall thickening or any lymphadenopathy. Her Right Kidney & Left Kidney size were normal with raised cortical echogenicity and intact corticomedullary junction. During 2nd admission, due to persistently abnormal KFT and worsened proteinuria with intact corticomedullary differentiation, renal biopsy was done; with histopathological features suggestive of Haemolytic Uremic Syndrome (Thrombotic Microangiopathy) with acute tubular injury with Immunofluorescence reports as follows: Fine granular deposits of C3 (1+) along the peripheral capillary walls and mesangium. No other significant deposit of IgG; IgA; IgM; C1q; λ; κ;

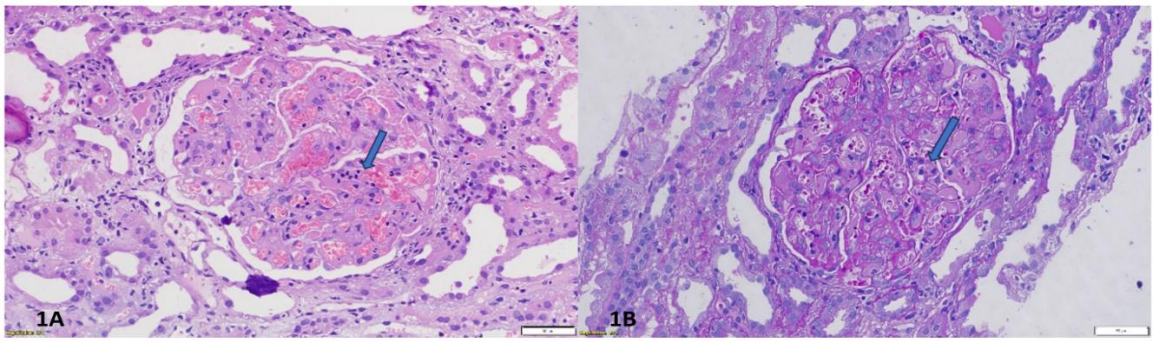

Figure 1A: Light microscopy on HE stain & 1B on PAS stain shows markedly congested, edematous and enlarged glomeruli with subendothelial edema & infiltration by PMN. No evidence of crescent formation or endocapillary proliferation was seen.

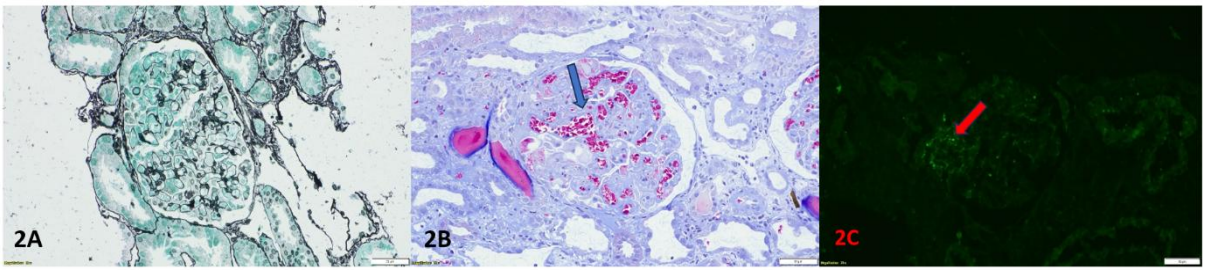

Figure 2A: shows on Massson Trichome stain 5-10% of tubulointerstitial compartment have chronic parenchymal damage.
Figure 2B: on silver methenamine stain shows splitting of basement membrane
Figure 2C: shows Fine granular deposits of C3 (1+) along the peripheral capillary walls and mesangium. No other significant deposit of IgG; IgA; IgM; C1q; λ; κ

Her repeat report of peripheral smear for schistocyte during second admission showed >10 schistocytes present in the smear; her corrected reticulocyte count was 2.5%. A final diagnosis of thrombotic microangiopathy (TMA) (probably infection associated or complement mediated or drug induced) was made along with differentials of other causes of TMA was kept in mind. She had a PLASMIC score of 2 with low probability of thrombotic thrombocytopenic purpura. A sample for anti-CFH antibody sent; reports were negative. Genetic testing for Complement factor H; Complement factor

I; MCP/ C3; Complement factor B etc could not be done due to resource limitation. During the course of second admission her liver & kidney function test (KFT) were deranged significantly with AST/ALT/ALP-324/300/534 IU/L with anaemia (Hb: 6.0g/dL); thrombocytopenia (50, 000/µL); Direct hyperbilirubinemia (T. BIL-6 mg/dL); deranged KFT (S. Cr: 5.8 mg/dl). Hence ATT was stopped & patient was referred to other hospital for plasma exchange as a treatment for TMA as facilities for plasma exchange as well as eculizumab was not available in our hospital.

3. Discussion

Thrombotic microangiopathy (TMA) is characterised by abnormalities in the vessel wall of arterioles and capillaries leading to microvascular thrombosis. It is mainly a pathologic diagnosis made by tissue biopsy, typically a kidney biopsy & commonly inferred from the observation of microangiopathic hemolytic anaemia and thrombocytopenia in the appropriate clinical setting.[4] MAHA or microangiopathic hemolytic anaemia is non-immune hemolysis (ie, Coombs-negative hemolysis) resulting from intravascular red blood cell fragmentation that produces schistocytes on the peripheral blood smear. Characteristic laboratory feature of MAHA is a negative direct antiglobulin (Coombs) test (DAT), an increased lactate dehydrogenase (LDH), increased indirect bilirubin, low haptoglobin level.[1, 4] TMA can be broadly classified as ADAMTS13 associated TMA (TTP); complement associated TMA; Metabolic associated TMA; Infection associated TMA; pregnancy associated TMA; drug induced TMA; autoimmune associated TMA; transplant associated and malignancy associated TMA.[1, 5] Endothelial injuries with associated platelet activation and consumption contribute to microvascular thrombosis formation, tissue ischemia, and subsequent end-organ injury.

Diverse pathogens, including bacteria, viruses, and fungi, are associated with infection associated TMA. Most common association of infection associated TMA is Shiga toxin mediated TMA (ST-TMA). Other important causes are other gram-positive bacteria, chlamydia, brucella, clostridium, Leptospira, mycobacteria; amongst viruses HIV, EBV, CMV, Dengue Virus, Parvo B19 are important. Aspergillus, blastomycosis, candida, malaria, babesia are also evidenced to be associated with TMA. EHEC; O157: H7 associated shiga like toxin & Shiga toxin associated TMA are the most common causes of infection associated TMA. Most but not all cases of Stx-HUS (about 80%) have prodromal diarrhea.[6] In our case the patient did not have any complain of diarrhoea; to correlate further we sent viral serology, a stool examination for ST toxin and stool culture, which were negative. Her tuberculin skin test was 25 (positive) without any previous history of tuberculosis. Her USG abdomen was suggestive of multiple necrotic mesenteric lymph node with ileocecal junction thickening with mild low SAAG high protein ascites with ADA value of 87, suggestive of tubercular ascites. Also considering her negative autoimmune profile, normal complement level, normal anti CFH level and on the basis of other investigations, we made a diagnosis of Thrombotic microangiopathy due to infection likely to be due to abdominal and peritoneal tuberculosis & started ATT.

The patient did not have any clinical presentation of neurological involvement and PLASMIC Score was 2; so, the possibility of TTP was low. Patient's vit B12 level was low initially, making a possibility of metabolism associated TMA, [7] however the evidence of hemolysis was persistent even after vit B12 supplementation, hence metabolism associated TMA was less likely diagnosis. She had no history of long-term drug intake. The idiosyncratic immune-mediated drug induced TMA (DITMA) presents acutely and is characterized by the production of reactive antibodies after the exposure to the drug and related to abnormal susceptibility/ hypersensitivity to it. The cumulative dose dependant DITMA is due to progressive blockade of different pathways involved in maintenance of physiological endothelial homeostasis.6 DITMA caused by direct dose-dependent drug toxicity are characterized by acute or subacute onset together with systemic features of initial or prolonged exposure to the drug[6]. In our case, Rifampicin was started after the initial presentation in 1st admission & she was discharged with improved KFT, LFT, CBC while she was still on rifampicin. Patients condition worsened progressively even after rifampicin was withheld in 2nd admission. A possibility of complement mediated TMA was kept in mind. C3, C4 levels were normal as shown in table 1 (although C3; C4 levels have very low sensitivity of 30% and low specificity in detecting complement mediated-TMA.).[9, 10] A sample for anti-CFH antibody (most common cause of complement mediated - TMA) was sent; reports were negative. Genetic testing for Complement factor H; Complement factor H I; MCP/ C3; Complement factor B could not be done due to resource limitation. However, the characteristic renal biopsy finding of complement mediated TMA i. e. deposition of predominantly C4d, C5b to C9 was not there for this patient.[10] TB as an infection to cause TMA is rarely detected with evidence of few case reports only available in the past. The mechanism of TMA induced by TB infection is not clearly understood, but direct endothelial injury may be involved. Toscano et al suggested that the pathogenesis of TTP might be increased pro-coagulant activity of interleukin 1 (IL-1) on endothelial cells.[11] Lu et al reported that tuberculous pleural and ascitic fluids contain high plasminogen activator inhibitor-1 (PAI-1) levels, which lead to reduced fibrinolytic activity. This change in fibrinolytic characteristics might affect the endothelial cell membrane.[12] However, in our case the possibility of TB to manifest as precipitating factor of Complement mediated TMA and cumulative dose dependant drug induced TMA due to rifampicin could not be commented upon due to scarcity of evidences to confirm complement association. In a nutshell, Tuberculosis associated thrombotic microangiopathy is although a rare entity, but should be also kept in mind especially in TB endemic areas. Continuation of ATT along with plasma exchange is usually effective in treating these patients.

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