Case Report

iMedPub Journals
http://www.imedpub.com

Medical Case Reports
ISSN 2471-8041

2021
Vol. 7 No. 4

Thrombotic Microangiopathy in COVID-19 and its Association with Complement Classical Pathway

Javeria Chughtai*, Imtiaz Salman, Aamir Zunaira, Ahmad Shehzad, Mubarak Muhammed, Saeed Faiza, Alam Ashar, Memon Shoukat, Tariq Sobia

Nephrology Department, The Indus Hospital Korangi Crossing Karachi, Pakistan

***Corresponding author:** Javeria Chughtai, Nephrology Department, The Indus Hospital Korangi Crossing Karachi, Pakistan, Tel: +92 21 3511 2709; E-mail: javeriachaghtai@gmail.com

Received date: April 09, 2021; **Accepted date:** April 23, 2021; **Published date:** April 30, 2021

Citation: Chughtai J, Salman I, Zunaira A, Shehzad A, Muhammed M, et al. (2021) Thrombotic Microangiopathy in COVID-19 and its Association with Complement Classical Pathway. Med Case Rep Vol.7 No.4.

Abstract

COVID-19 pandemic has affected the whole world in last 1 year with catastrophic effects. This virus has been commonly associated with thromboembolic tendency, resulting in pulmonary embolism, cerebrovascular accidents, myocardial infarctions and acral Cyanosis. Acute kidney injury is also very common amongst patients with COVID-19 infection, mostly due to pre-renal AKI, Acute tubular necrosis or collapsing glomerulopathy. Renal injury due to thrombotic microangiopathy and cortical necrosis is not a common finding in COVID-19 infections. Here we are reporting a case of young female with Critical COVID Pneumonitis and Cytokine release syndrome, who developed AKI due severe TMA and cortical necrosis.

Keywords: COVID-19; Thrombotic microangiopathy; Complement system; Atypical HUS; Classical pathway; Acute kidney Injury

Introduction

Acute kidney injury (AKI) is one of the commonest complications in COVID-19 infection. Causes of AKI in COVID-19 vary from Pre-renal AKI due to volume depletion, toxic or ischemic acute tubular necrosis, collapsing glomerulopathy, drugs toxicity. AKI due to thrombotic microangiopathy is an uncommon happening, reported only in few case reports [1]. But post mortem studies in majority of COVID-19 show fibrin deposition and florid microvascular thrombosis in lungs. In this case, presence of hemolytic anemia, thrombocytopenia, acute kidney injury and circulating schistocytes prompted us to consider hemolytic uremic syn - drome or Thrombotic thrombocytopenic Purpura. Predominant renal failure in this case was more suggestive of atypical HUS but the unique renal histopathology findings and normal complement levels favor classical pathway associated thrombotic microangiopathy. Moreover, there is no such published case report till date from Pakistan.

Case History

A 38 years Housewife, primigravida with 8 month gestational amenorrhea, presented in our emergency room on 23rd July with history of Cough and difficulty of breathing for last 5 days, progressively worsening and Pervaginal bleeding for last 1 day. On presentation, patient had BP of 180/100 mmHg, heart rate 110 per minute, respiratory rate 40 per minute and oxygen saturation of 80% on ambient air. She had bilateral coarse crepitation in mid and lower zones of chest. The abdomen was tense and tender with gravid uterus and along with this, she had heavy per- vaginal bleeding. General physical and systemic examination was otherwise unremarkable. After initial assessment, diagnosis of abruption placentae, Critical COVID Pneumonitis with Cytokine release syndrome (CRS) was made. She was rushed to operation room for an emergency Caesarian section and a non-alive baby of 1.25 kg was delivered. After Caesarian section, she was shifted to COVID-19 ICU in intubated state. She was started with Injection Ceftriaxone, steroids and Remdesivir.

Approximately 48 hours after delivery, there was progressive decline in her urine output followed by anuria, along with sharp rise in her serum creatinine and blood pressure Further workup showed rapidly dropping hemoglobin and platelet count with 1%-2% Schistocytes on peripheral film, significantly high lactate dehydrogenase (LDH) and normal coagulation (Table 1). Hence, Initial impression of postpartum HUS was made and she was supported with hemodialysis and plasma exchange (PLEX) was also initiated. For the Initial two days plasma infusion was done as plasma exchange service was not available due to lock down situation. Then 5 daily sessions of plasma exchange were done along with methylprednisolone pulse therapy. Regular sessions of hemodialysis were also done on account of acute renal shut down. Due to renal dysfunction, Remdesivir was stopped. Renal biopsy was done which comprised of two cores of renal tissue, consisting of cortex revealing patchy cortical infarction.

The Specimen included 22 glomeruli, of these, 4 were infarcted, one showed ischemic solidification, rest showed fibrin thrombi in capillary lumina. Part of wall of artery was included, which was unremarkable. No significant tubular atrophy was seen. Immunofluorescence was done on fresh frozen tissue and showed diffused positivity in mesangium and along vessel walls of IgM and C1q (++each), while rest of the panel was negative (**Figures 1 and 2**).

Table 1 Laboratory Parameters

Dailyevent	Day1	Day 2	Day 3	Day4	Day5	Day 6	Day 7	Day 8	Day9	Day 10	Day 11
Laboratory Parameters											
Hb(gm/dl)	15.4	11.7	12	6.9	10.2	11.1	10.8	10.5	10.2	8.8	11.6
WBC	23	34.5	48	23.9	22	30	37.6	37.7	35.9	38.6	50.6
PLT	273	87	63	115	156	172	212	282	310	289	346
Cr(mg/dl)	0.8	1.6	1.9	1.9	1.4	1.9	1.49	3.1	2.4	-	2.79
LDH(U/L)	905	-	4768	3296	2201	1085	827	798	649	559	931
Ferritin(ng/ml)	275	-	-	-	-	-	-	-	-	-	-
CRP(mg/dl)	22	256	-	-	302	-	-	-	-	-	-
D-Dimer(ng/ml)	1.74	-	-	-	-	>4	-	-	-	-	-
Prolacitonin(ng/ml)	0.9	-	-	-	1.07	-	-	-	-	-	-
PT (sec) /INR	10.6/1.0	11.0/1.05	10.4/0.9	-	-	10.8/1.03	11.7/1.1	11.7/1.1	-	-	-
aPTT(sec)	38.9	27.7	35.9	-	-	-	27	28.5	-	-	-
Total bilirubin(mg/dl)	0.4	-	0.6	-	1.2	0.7	-	-	-	-	-
Direct bilirubin(mg/dl)	0.2	-	0.36	-	0.8	-	-	-	-	-	-
SGPT(U/L)	39	-	105	-	71	40	-	-	-	-	-
Retic count(%)	-	-	-	7.50%	3.90%	-	-	-	-	-	-
IL-6(pg/ml)	66.2	-	-	-	-	-	-	-	-	-	-
ANA	-	-	-	-	-	-	+2(speckled)	-	-	-	-
AntiDsDNA	-	-	-	-	-	-	Negative	-	-	-	-
AcIIgMAB(MPL) andIgGAb(GPL)	-	-	-	-	-	-	Negative	-	-	-	-
LA(sec)	-	-	-	-	-	-	Weak positive	-	-	-	-
ENA	-	-	-	-	-	-	Negative	-	-	-	-
C3(g/L		-	-	-	-	-	0.85	-	-	-	-
C4g/L		-	-	-	-	-	0.17	-	-	-	-

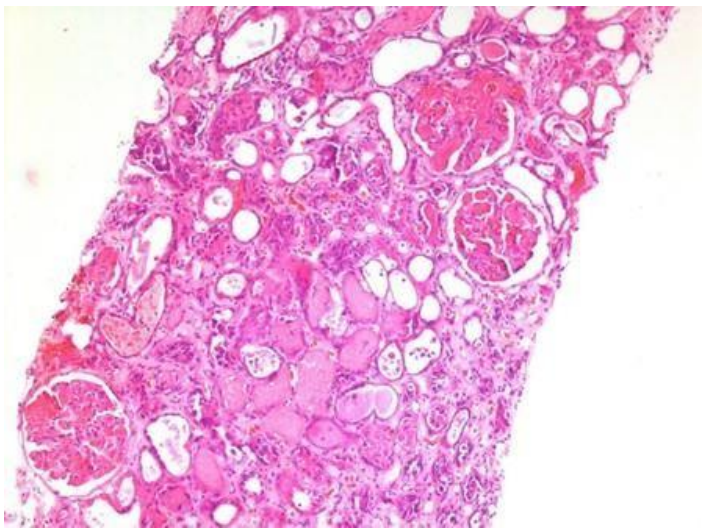

Figure 1 Renal biopsy showing fibrin thrombi in capillary lumina

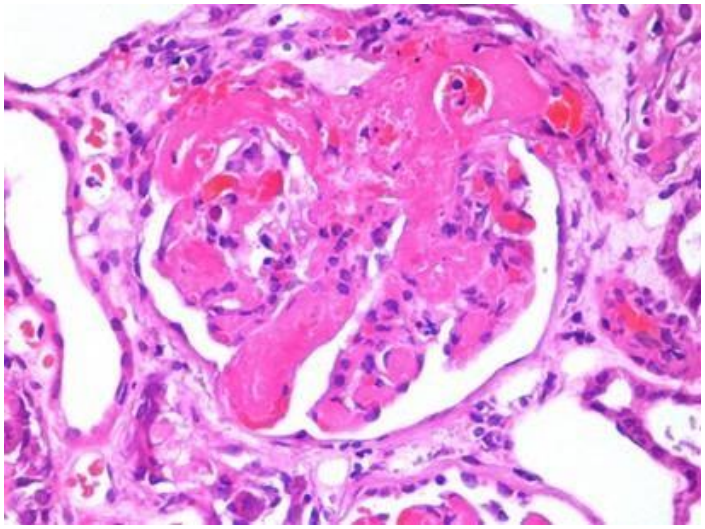

Figure 2 Renal biopsy

Patient's blood indices significantly improved with plasma exchange. Thoughsherequiredpersistenthighventrequirements.

During t his period, she developed l eft hand ecchymosis with left thumb gangrene. Ultrasound Doppler showed normal flow in left brachial and ulnar arteries, but no flow in Left radial artery. As platelet counts were stabilized and had rapidly rising D-Dimer, therefore renal adjusted therapeutic Enoxaparin was started. Due to rising Procalcitonin and white cell count, broad spectrum antibiotics were started after sending cultures. At 10th day of admission, patient became progressively hypoxic and hypotensive requiring vasopressor support and maximal ventilator support. At 11th day, she developed sudden hypoxia, hypotension with new high grade fever, chest X-ray suggestive of new dense consolidation. She eventually went into cardiac arrest and could not be revived after resuscitation. Death was declared to her attendant.

Discussion

Acute kidney injury is one of the devastating complications in patients infected with COVID-19 [2]. The etiology of acute kidney injury in COVID-19 reportedly ranged from pre-renal azotemia, acute tubular necrosis (ATN), to collapsing glomerulopathy [3]. When clinical examination and l aboratory findings suggest the presence of hemolysis along with thrombocytopenia and acute kidney injury, treating physician should consider Microangiopathic hemolytic anemia in the differential diagnosis. SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the heart, intestine, kidney, and lung. ACE2 receptors are also expressed by endothelial cells [4]. Montel and Prado showed a direct effect of SARS-CoV-2 on engineered human blood vessel organoids *in vitro* [5].

There are similarities and differences between the pattern of coagulation abnormalities in disseminated intravascular coagulation (DIC), Hemolytic uremic syndrome (HUS), and Thrombotic thrombocytopenic purpura (TTP) and Antiphospholipid antibody syndrome (APS). Therefore it is important to differentiate this syndrome from Covid-19 endothelial injury and pattern of coagulation abnormalities (Table 2).

Table 2 Renal biopsy showing fibrin thrombi in capillary lumina

Clinical condition	Primary cause and targetofcoagulopathy	Platelet count	D-dimer	PT/aPTT	fibrinogen	Anti-thrombin	Activated complementsystem/VWF	Antiphospholipid antibody	Inflammatory cytokines (IL-1β, IL-6)
COVID-19	Macrophage/ endothelial cell	↑↓	↑	→	↑	→	+	+	↑
DIC/	Macrophage/ endothelial cell	↓	↑	↑	→↓	↓	–	–	↑

SIC									
APS	Antiphos-pho-lipid antibody	↓	→	PT →aPTT ↑	→	→	–	–	–
TMA (aHUS/TTP	Comple-ment system/ AD-	↓	→	→	→	→	aHUS+/– TTP –/+	+	–

Our patient developed sudden anuria associated with surge in blood pressures, active hemolysis and thrombocytopenia. There was no convincing evidence of superimposed bacterial sepsis, neither deranged coagulation, rendering possibility of DIC least likely. In contrast, Presence of schistocytes in peripheral blood smear, active hemolysis and thrombocytopenia favored diagnosis of thrombotic microangiopathy. Presence of normal complement levels and renal biopsy staining of C1q and IgM indicates activation of classic complement pathway instead of alternative complement pathway. This contradicted our first impression postpartum HUS, which is mediated through alternative pathway [6].

Moreover we had this combination of rapidly rising D-dimer, Raised CRP, ferritin, LDH and IL-6, which is unique to COVID-19 infection [7]. COVID-19 patients may have anti phospholipid antibodies positive and our patient too had weak positive lupus anticoagulant [8]. Though her ANA was positive, clinical picture was not typical of SLE flare and associated TMA. Renal biopsy did not show any other feature typical of Lupus nephritis and rest of the autoimmune serology along with complement levels was also normal.

Presence of negative anticardiolipin antibodies, normal aPTT and raised D-Dimer exclude possibility of active Antiphospholipid syndrome in our patient. Unfortunately, we do not have fibrinogen and antithrombin levels available for this patient to support our diagnosis further.

We did not have facility to check ADMATS 13, Complement Factor H, Complement Factor I and similar assay to further distinguish among different spectrum of TMA. COVID-19 virus mediates inflammatory response via all 3 complements pathways [9-10]. Classical findings of TMA in renal biopsy with strong C1q and IgM positivity is a convincing evidence of classical pathway mediated TMA, which was possibly triggered by COVID-19 infection in our case.

Conclusion

Acute kidney injury is also very common amongst patients with COVID-19 infection, mostly due to pre-renal AKI, acute tubular necrosis or collapsing glomerulopathy. Renal injury due to thrombotic microangiopathy and cortical necrosis is not a common finding in COVID-19 infections.

References

1. Jhaveri KD, Meir LR, Chang BS, Parikh R, Wanchoo R, et al. (2020) Thrombotic microangiopathy in apatient with COVID-19. Kidney Int 98(2):509-512.
2. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, et al. (2020) Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 98(1):209-218.
3. Mohamed MM, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, et al. (2020) Acute kidney injury associated with coronavirus disease in 2019 Urban New Orleans. Kidney 360(1):10-34067.
4. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, et al. (2005) Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 111(20):2605-10.
5. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, et al. (2020) Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 181(4):905-913.
6. Gupta M, Govindappagari S, Burwick RM (2020) Pregnancy-associated atypical hemolytic uremic syndrome: A systematic review. Obstet Gynecol 135(1):46-58.
7. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, et al. (2020) The unique characteristics of COVID-19 coagulopathy. Critical Care 24(1):1-8.
8. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, et al. (2020) Coagulopathy and antiphospholipid antibodies in patients with Covid-19 N Engl J Med. 382(17):38.
9. Java A, Apicelli AJ, Liszewski MK, Coler-Reilly A (2020) The complement system in COVID-19: Friend and foe?. JCI insight. 6:5(15).
10. Noris M, Benigni A, Remuzzi G (2020) The case of Complement activation in COVID-19 multiorgan impact. Kidney Int. 98(2):314-322.