Case Series

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Clinicopathological Parameters of Haemolytic Anaemia in COVID-19 Infection: A Series of Three Cases

Pathology Section

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) patients show various haematological abnormalities like cytopenia and coagulation disorders. Coronavirus can induce an inflammatory state, leading to extensive coagulation manifestations. Association between COVID-19, Autoimmune Haemolytic Anaemia (AIHA) and thrombotic state is still the subject of extensive research. In this study, three cases of haemolytic anaemia are discussed. First case was a 28-year-old female with a history of abruptio placentae who presented with complaints of generalised weakness and oliguria for five days. She was diagnosed as thrombotic microangiopathy based on peripheral smear finding of schistocytes and spherocytes and few polychromatophils and normal prothrombin time (International Normalised Ratio (INR)) with very high D-dimer levels on coagulation profile. Second case was of a 25-year-old female who presented with complaints of fatigue, rashes, dark urine, nausea and abdominal pain. She was diagnosed as a case of AIHA based on peripheral smear finding of Red Blood Cells (RBC) clumping and positive direct coomb test. Third case was of a two-month-old child who presented with respiratory distress and pallor. He was diagnosed as a case of haemolytic anaemia either due to direct effect of COVID-19 infection or Cytomegalovirus (CMV) and mycoplasma infection. Thus, COVID-19 infection can directly or indirectly lead to a wide spectrum of haemolytic manifestations and every patient with anaemia should be thoroughly investigated for early detection and treatment.

Keywords: Coronavirus disease, Haematological manifestations, Inflammation

INTRODUCTION

COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Patients present with fever, cough, myalgias and fatigue [1]. Anosmia and ageusia have also been found to be common symptoms. As COVID-19 emerged, many patients also presented with coagulation disorders [2]. It is presumed that COVID-19 infection directly and indirectly leads to haemolysis and cytopenia. The high levels of inflammation throughout the body in COVID-19 patients can cause excessive activation of the coagulation cascade leading to extensive coagulation manifestations.

Association between COVID-19, AIHA and thrombotic state is still less understood as available data is incomplete and still emerging. AIHA is an acquired haemolysis in which the host's immune system attacks its own red cell antigens. Serologically, cases are divided into warm, cold or mixed types [3]. Patients may present with symptoms of anaemia such as dizziness, tiredness and dyspnoea, or evidence of haemolysis with jaundice and dark urine. On a blood film, RBC agglutination and spherocytosis may be apparent. The reticulocyte count is usually increased but may be normal in cases of a very short duration of haemolysis or with an underlying bone marrow disorder [4].

There are several causes of AIHA. These include autoimmune, infections (bacterial, viral or parasitic), lymphoproliferative disorders and immunodeficiency states. Out of all viral infections, herpes virus especially Herpes Simplex Virus (HSV) is most notorious [5]. Previous, latent or manifested infection in the setting of COVID-19 builds on a milieu for complement and coagulation cascades to get activated unabated. The underlying mechanism of Multiple Organ Dysfunction (MOD) in COVID-19 leading to an outburst of deaths, still ill understood. Various hypothesises proposed under study are direct effect of the virus, cytokine storm, uncontrolled endothelial damage, and autoantibodies against the coronavirus which starts attacking various cells like RBCs and platelets leading to haemolysis, thrombocytopenia and subsequently MOD [6].

Present case series includes three known cases of COVID-19 who presented with haemolytic blood picture due to thrombotic microangiopathy, AIHA and COVID-19 viropathy, respectively.

CASE SERIES

Case 1

A 28-year-old female presented to emergency of Medicine Department with complaints of generalised weakness and reduced urine output for five days. She was admitted to medicine ward and her Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) test for COVID-19 came out to be positive. She had fever with mild cough one week back and a history of preterm vaginal delivery with abruptio placentae 10 days prior to admission. There were no co-morbidities, and her family history was insignificant. On examination there was pallor, but no hepatosplenomegaly or lymphadenopathy. Her Kidney Function Test (KFT) and Liver Function Test (LFT) was deranged, with alanine aminotransferase level of 145 IU/L, alkaline phosphatase level of 359 IU/L, serum urea of 194 mg/dL and serum creatinine of 10.6 mg/dL (Normal serum bilirubin, aspartate aminotransferase). Her inflammatory markers were elevated (HsCRP level of >150 mg/L). Her Complete Blood Count (CBC) showed low haemoglobin (Hb) of 8.3 gm/dL and platelet count of 78,000/mm^3 [Table/Fig-1,2].

Patient was started on dialysis and 3 units of Packed Cell Volume (PCV) were transfused. On examination of peripheral smear stained with May Grunwald-Giemsa (MGG), there was bicytopenia with reduced red cell mass. RBCs were normocytic normochromic with many schistocytes and spherocytes and few polychromatophils. There was neutrophilic leucocytosis with left shift. Picture was suggestive of thrombotic microangiopathy [Table/Fig-1,3]. Possibilities suggested were Disseminated Intravascular Coagulation (DIC) and atypical Haemolytic Uremic Syndrome (aHUS) and Thrombotic Thrombocytopenic Purpura (TTP), on further analysis coagulation profile showed normal prothrombin time (12 second) and INR (0.8) but very high D-dimer levels (75000 ng/mL), ruling out DIC [Table/Fig-2]. Final diagnosis given was aHUS/TTP. But low PLASMIC score of 3 {INR <1.5, absence of active cancer and no prior stem cell or organ transplantation}, meant low risk of severe ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1

motif, member 13) deficiency, thus making aHUS most probable diagnosis. Where PLASMIC score was calculated based on the following parameters: Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, MCV, INR, and Creatinine. Her coomb test was negative. She was not investigated for autoimmune status and other viral infections (like Cytomegalovirus (CMV) or mycoplasma). For further management, she was referred out to a non COVID-19 centre when she turned COVID negative.

Case 2

A 25-year-old female presented with complaints of fatigue, rashes, dark urine, nausea and abdominal pain for last seven days. Rashes were seen on the chest and upper back. Abdominal pain was dull, continuous and in right hypochondriac region. On examination, she had icterus and anasarca. She gave a history of anosmia, cough and fever for seven days, 12 days back and became COVID-19 negative five days back. Her initial investigation showed anaemia (Hb of 9.6 gm/dL) and unconjugated hyperbilirubinemia (total and direct bilirubin level being 34.32 mg/dL and 12.23 mg/dL, respectively), and deranged LFT [Table/Fig-1,2]. On peripheral smear examination, there was neutrophilic leucocytosis with RBC clumping in the background. RBCs were predominately normocytic normochromic with marked anisopoikilocytosis, few microcytic hypochromic cells, few target cells, schistocytes, elliptical cells and occasional leptocytes were seen [Table/Fig-1,3]. Direct Coomb's test (DCT) using polyclonal antisera showed grade 2 RBC agglutination. Her pre and post-incubation at 4°C, CBC and peripheral smear showed significant differences [Table/Fig-1,3]. So, a final diagnosis of AIHA (cold agglutinin induced) was made based on peripheral smear findings and positive DCT test.

Flowcytometry showed T-cell Lymphopenia (absolute T-cell count being 540/mm3) (Reference: 939-3572/mm^3) and down regulation of Human Leukocyte Antigen-DR isotype (HLA-DR) on monocytic population with absence of Natural Killer cell (NK cell) population [7]. Ultrasound with doppler showed evidence of Hepatitis with hepatomegaly. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Cholangiopancreatography (MRCP) were suggestive of fatty liver and acalculous cholecystitis [Table/Fig-3]. Serology was negative for Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E, Epstein-Barr Virus (EBV), CMV and Human Immunodeficiency Virus (HIV). But she was found to be positive for IgG Hepatitis A virus EBV, CMV and *Mycoplasma* on repeat testing after three weeks. After starting steroid therapy (Prednisolone 5 mg daily) for five days patient improved both clinically and biochemically. Liver biopsy was performed after patient got stabilised and showed features of acute exacerbation of pre-existing hepatitis with submassive hepatic necrosis. Patient improved on further follow-up for next three months but suddenly deteriorated and succumbed to her illness.

Case 3

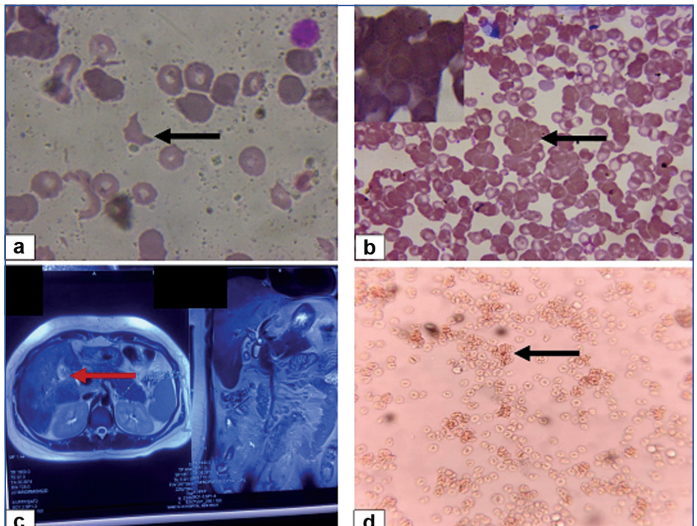
A two-month-old COVID-19 positive child presented with shortness of breath and generalised weakness for 10 days. There were no co-morbidities or significant family history. On examination, there was pallor and hepatosplenomegaly. Initial investigation showed anaemia and neutrophilic leucocytosis, which persisted on subsequent work-up [Table/Fig-1,2]. On peripheral smear, there was neutrophilic leucocytosis (absolute neutrophil count of 71,604/mm^3) with reduced RBC mass (2.12 million/mm^3). RBCs were predominately normocytic normochromic with moderate anisopoikilocytosis, fair number of schistocytes, occasional tear drop cells and target cells along with spherocytes were noted [Table/Fig-4]. His chest radiograph showed ground glass opacity in bilateral upper left and right perihilar region suggestive of indeterminate COVID-19 [Table/Fig-4]. In view of persistent leucocytosis and anaemia despite multiple transfusion, patient underwent bone marrow examination which showed pauci

Demography		Case 1				Case 2					Case 3		
		28 Y/Female				25 Y/Female					2 Months/Male		
Clinical presentation		Preterm delivery with abruption placentae+Pallor				Icterus+Fever+Rashes+Fatigue +Anasarca					Bronchiolitis+Pallor+Hepatosplenomegaly+Umbilical Hernia		
CBC	Date	14/8	18/8	21/8	23/8	12/10	30/10	6/11	30/11	16/12	1/12	4/12	14/12
	Hb (g/dL)	8.3	6.1	7.7	8.2	9.6	9.8	10.3	13.4	12	8.6	7.6	6.4
	TLC (/mm^3)	9,470	14,730	12,500	10,120	5,400	6,600	8,200	20,100	17,990	91,800	66,590	62,120
	Platelets (/mm^3)	78,000	68,000	1,38,000	1,94,000	1,52,000	1,59,000	1,65,000	1,80,000	1,13,00	4,43,000	3,08,000	85,000
	RBC count (million/mm^3)	-	2.09	-	-	-	-	-	Pre-incubation 3.14	Post-incubation 2.74	-	-	2.12
	HCT (%)	-	19.5	-	-	-	-	-	28	25.9	-	-	20.6
	MCV (fL)	-	93.3	-	-	-	-	-	92	94.5	-	-	97.2
	MCH (pg)	-	29.2	-	-	-	-	-	38	44.2	-	-	30.2
	MCHC (g/dL)	-	31.3	-	-	-	-	-	41	46.7	-	-	31.1
	Delta Hb (%)	-	-	-	-	-	-	-	1.2	-	-	-	-
	Retic count (%)	-	2	-	-	-	-	-	5.78	-	4.14	-	-
Peripheral smear		Bicytopenia+neutrophilic leukocytosis+schistocytes and spherocytes and few polychromatophils				RBC clumping increased on incubation+neutrophilic leukocytosis+thrombocytopenia+schistocytes, elliptical cells and occasional leptocytes					Neutrophilic leukocytosis+schistocytes, occasional tear drop, spherocytes and target cells		
DCT		Negative				Weak positive (2+)					Negative		
Bone marrow		N.A				N.A					Mildly hypocellular smear for age with erythroblastopenia with trilineage dyspoesis free of neoplastic or infective disease. Myelogram showed Er 8, My 55, MM 54, Band 34, P2 4,L 22, E 1, plasma cells 2 (200 cells)		

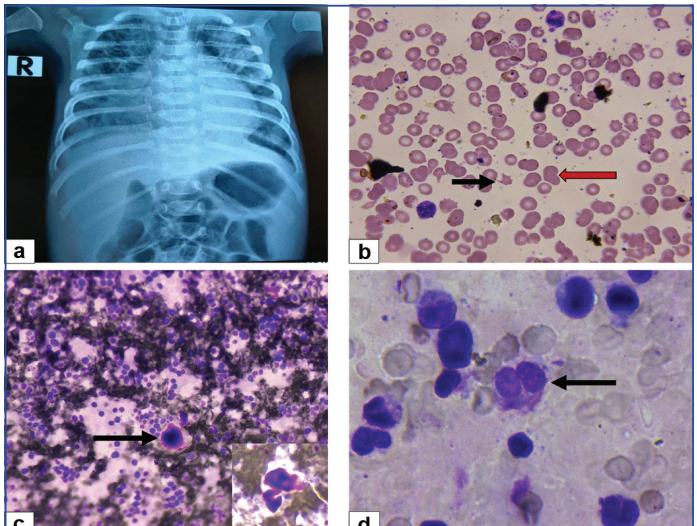
[Table/Fig-1]: Complete clinical and haematological work-up for haemolytic anaemia in COVID-19 positive patients.
CBC: Complete blood bount; Hb: Haemoglobin; TLC: Total leukocyte count; RBC: Red blood cell; HCT: Haematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular hemoglobin concentration; DCT: Direct coombs test

Clinical presentation		Case 1				Case 2							Case 3		
LFT	Date	14/8	18/8	21/8	23/8	12/10	30/10	6/11	12/11	21/11	5/12	13/12	1/12	4/12	14/12
	Total Bilirubin (mg/dL)	0.8	0.8	-	-	8.52	34.32	20.4	14.15	21.80	26	12.05	0.3	0.4	2.2
	Direct Bilirubin (mg/dL)	0.4	0.5	-	-	-	12.23	8.48	-	-	17.6	-	0.2	0	0.6
	AST (IU/L)	34	33	39	-	568	682	298	225	140	124	128	21	34	12
	ALT (IU/L)	145	52	36	-	447	516	287	147	55	131	183	16	20	17
	ALP (IU/L)	359	324	302	-	178	160	144	131	120	275	286	-	-	-
	GGT (IU/L)	-			-	-	52	-	-	-	-	-	-	-	-
	Albumin (g/dL)	-			-	4.9	3.55	-	-	3.8	3.3	-	-	-	2.6
KFT	S. Urea (mg/dL)	194	156	170	-	-	-	-	-	-	-	-	21	23	45
	S.Creatinine (mg/dL)	10.6	12.1	9.6	-	-	-	-	-	-	-	-	0.2	0.15	0.2
Flowcytometry		NA				T-cell Lymphopenia, downregulation of HLA-DR on monocytic population with Nil NK cell population.							NA		
Liver biopsy		NA				Acute on chronic hepatitis with features of submassive hepatic necrosis.							NA		
Radiology		NA				USG: Evidence of Hepatitis with hepatomegaly MRI: Geographical areas of altered signal intensity involving bilateral lobes suggestive of fatty infiltration was seen and the gall bladder appeared partially distended with irregular and oedematous thickened walls suggestive of Acalculous cholecystitis.							Chest x-ray: Ground glass opacity in B/L upper left and right perihilar region. Suggestive of Indeterminate COVID-19		
Coagulation profile	Date	14/8	18/8	21/8	23/8	12/10		5/12	13/12				1/12	4/12	14/12
	D-dimer (ng/mL)	75,000	-	-	-	-	-	-	-				2728	4792	783
	PT (sec)	12	-	-	-	17.1	-	22.9	22.7				14.8	11.6	13.9
	INR	0.8	-	-	-	1.93	-	1.75	1.81				1.236	0.9	1.1
S.LDH (U/L)		2,223	-	884	-	-	-	-	-				259	-	-
HsCRP (mg/L)		>150	-	46.2	-	-	-	-	-				-	-	-
S.Ferritin (ng/mL)		-	-	-	-	-	-	-	-				-	-	-
Haptoglobin (g/L)		1.8	-	-	-	-	-	0.09	-				-	-	-
Autoimmune profile		-	-	-	-	ANA, dsDNA, Antismooth muscle antibody, Antiliver-kidney microsomal antibody negative							-	-	-
Serology	Positive	-				IgG HAV, CMV,IgG EBV, IgG Mycoplasma							IgM CMV and *Mycoplasma*		
	Negative	-				IgM HAV, IgM HCVIgG, IgM HEV, HIV, EBV, HBsAg, IgM CMV, IgM mycoplasma							-		
Final diagnosis		TTP/aHUS				AIHA							Haemolytic anaemia		

[Table/Fig-2]: Complete biochemical and radiological work-up for haemolytic anaemia in COVID-19 positive patients.
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; PT: Prothrombin time; INR: International normalised ratio; LDH: Lactate dehydrogenase; CRP: C-reactive protein; ANA: Antinuclear antibodies; DNA: Deoxyribonucleic acid; HAV: Hepatitis A virus; EBV: Epstein-barr virus; CMV: Cytomegalo virus; TTP: Thrombotic thrombocytopenic purpura; aHUS: Atypical haemolytic uremic syndrome; AIHA: Autoimmune haemolytic anaemia; USG: Ultrasound; MRI: Magnetic resonance imaging; B/L: Bilateral



[Table/Fig-3]: a) Case 1: Peripheral smear: showing Schistocytes (MGG 1000X); b) Case 2: Peripheral smear: RBC agglutination (MGG 400X), inset (MGG 600X); c) Case 2: MRI: suggestive of fatty infiltration (red arrow) and Acalculous cholecystitis; d) Case 2: DCT: Positive test (100X).



[Table/Fig-4]: a) Case 3: X-ray chest: showing bilateral lung infiltrates; b) Peripheral smear: showing Spherocyte (red arrow) and schistocytes (black arrow) (MGG 400X); c) Bone marrow aspirate: Dyspoietic megakaryocyte (MGG 400X); d) Bone marrow aspirate: Binucleate myeloid precursor (MGG 1000X).

particulate hypocellular marrow. Erythroid series was markedly suppressed and showed predominately normoblastic erythroid reaction. Myeloid series showed mild myelodyspoesis in the form of binucleation, doughnut cells, few immature precursors with hypogranulation. Megakaryocytes were adequate in number and showed features of megakaryodyspoesis in form of small dwarf forms with hypolobation [Table/Fig-4]. His serology showed positive IgM CMV and *Mycoplasma pneumoniae*. Final diagnosis was haemolytic blood picture (either due to direct effect of COVID-19 infection or CMV and *Mycoplasma* induced), neutrophilic leucocytosis and mildly hypocellular marrow for age with erythroblastopenia and trilineage dyspoesis due to congenital CMV infection. Unfortunately, by the time detailed work-up was concluded patient succumbed to his illness.

DISCUSSION

While the main target of COVID-19 remains the lung, with respiratory failure and acute respiratory distress syndrome seen in severe cases, extrapulmonary complications are now increasingly reported. Many patients present with various haematological manifestations like cytopenia (anaemia, lymphopenia and thrombocytopenia) and coagulation disorders. Araya S et al., studied 334 admitted COVID-19 patients for haematological abnormalities. They reported any cytopenia and pancytopenia in 41% and 1.8% patients, respectively. Anaemia, thrombocytopenia, and leukopenia was seen in 24.9%, 21.6%, and 5.4% patients, respectively. Lymphopenia (72.2%) was the most common haematological abnormality [8]. It is presumed that COVID-19 infection directly and indirectly leads to haemolysis and cytopenia. Haemolytic anaemia can also occur due to other aetiological agents like accompanying CMV or *Mycoplasma* infection and it is very important to detect such cases. The high level of inflammatory cytokines throughout the body and direct endothelial injury causes excessive activation of the coagulation and complement cascade, leading to thrombotic complications [9].

First case was of a 28-year-old female, who presented with complaints of generalised weakness and oliguria and antecedent history of preterm vaginal delivery with abruptio placentae 10 days prior to current complaints. On detailed work-up, she was diagnosed as thrombotic microangiopathy with neutrophilic leucocytosis, differentials being TTP, aHUS and DIC. DIC was ruled out as Prothrombin Time test (PT) and INR were within normal limits with extremely high D-dimer levels (75000 ng/mL). Thus, most probable diagnosis being aHUS/TTP. They can be differentiated accurately only after ADAMTS13 activity levels, values <10% indicative of TTP. (Unfortunately, that couldn't be done as patient was transferred to another institute). But low PLASMIC score of 3 (INR <1.5, absence of active cancer and no prior stem cell or organ transplantation), meant low risk of severe ADAMTS13 deficiency, thus making aHUS most probable diagnosis. In a review article conducted for cases between 1964-2002, it was found that 13% of thrombotic microangiopathic patients were pregnant [10]. As pregnancy alone is hypercoagulable state, superimposed abruptio placentae and COVID-19 might act as an amplifier.

Two studies reported by Ville S et al., and Altowyan E et al., were compared to our case [11,12] [Table/Fig-5]. Ville S et al., reported a case of aHUS with COVID-19 infection where a 28-year-old female presented with recurrent, relapsing, and remitting haemolysis since childhood [11]. This got exaggerated in current COVID-19 pandemic when she presented with extrauterine pregnancy. This case is an illustration that COVID-19 is to be added to the list of the potential triggers of aHUS relapse. In this setting, the deleterious effect of the COVID-19 may arise from: (i) a direct toxic effect on endothelial cells, as suggested by various autopsy studies; and/or (ii) a complement activation with ultimately complement-mediated endothelial damage, most particularly in patients with a constitutional defect in complement regulation, as in the patient presented herein. Case 1 had similar clinical and laboratory findings with low PLASMIC score of 3 [Table/Fig-5].

Clinical presentation	Current study (1st case)	Ville S et al., [11]	Altowyan E et al., [12]
History	Preterm delivery, abruptio placentae, oliguria	Know case of aHUS, fever, headache	Epigastric pain, nausea, vomiting
CBC	Anaemia, thrombocytopenia	Anaemia, thrombocytopenia	Anaemia, thrombocytopenia
PS	Haemolytic anaemia	Haemolytic anaemia	Haemolytic anaemia
LFT	Deranged	Deranged	Deranged
KFT	Deranged	Deranged	Normal
Coagulation	Normal PT/INR D-dimer 75000 ng/mL	D-dimer 512 ng/mL	Normal PT/INR D-dimer 7290 ng/mL
Inflammatory markers (IL-6, LDH, CRP)	Elevated	NA	Elevated
PLASMIC score (Platelet count, S Creatinine, P/O haemolysis, INR, MCV, No active cancer, No stem cell or organ transplant	Low (3)	N. A	High (6)

[Table/Fig-5]: TTP/aHUS comparison with available literature [11,12].
CBC: Complete blood count; LFT: Liver function test; KFT: Kidney function test; IL-6: Interleukin; LDH: Lactate dehydrogenase; CRP: C-reactive protein

Altowyan E et al., reported a 39-year-old man who presented with a history of epigastric pain, nausea and vomiting for approximately seven days before admission [12]. He was diagnosed as TTP due to thrombocytopenia, microangiopathic haemolytic anaemia and schistocytes in the peripheral blood film. The PLASMIC score was 6, which meant that the patient had a high risk of severe ADAMTS 13 deficiency. These findings were in conjunction with the present study except there was no prothrombotic risk factor in this case and PLASMIC score (6) was high [Table/Fig-5].

Autoimmune manifestations of COVID-19 includes, autoimmune thrombocytopenia, Guillain–Barre and antiphospholipid syndrome. AIHA is an unusual finding. AIHA is an acquired haemolysis in which the host's immune system attacks its own red cell antigens. Cold agglutinins are formed when B cells produce IgM autoantibodies with an antigen antibody reaction between 0 to 4°C. These autoantibodies are capable of agglutinating red blood cells, causing complement-mediated extravascular haemolysis and resulting in an AIHA. When cold agglutinin autoantibodies are produced in association with an underlying hematologic malignancy or infection, this is called cold agglutinin syndrome [13]. COVID-19 can be associated with cold agglutinin syndrome, just like *Mycoplasma pneumoniae*, EBV, and CMV [14,15].

Second case was a 25-year-old female who presented with complaints of fatigue, fever, rashes, icterus and anasarca and final diagnosis given was AIHA induced by cold agglutinin. As patient was positive for IgG HAV, IgG EBV and IgG CMV it is difficult to rule out infective cause of AIHA.

Third case was a two-month-old child who presented with respiratory distress and pallor. On examination, hepatosplenomegaly was also found. Haemogram and blood picture was suggestive of neutrophilic leucocytosis with haemolysis while bone marrow examination showed erythroblastopenia with trilineage dyspoiesis. Child had a COVID-19 positive immune modulated state with CMV and *Mycoplasma* infection concomitantly. Few case reports were compared to present cases (case 2 and 3) of haemolytic anaemia [Table/Fig-6] [4,16,17].

Maslov DV et al., reported a 48-year-old COVID-19 positive male whose neurological status declined three hours after admission

Clinical presentation	2nd Case	3rd Case	Maslov DV et al., [16]	Capes A et.al., [17]	Jawed M et al., [4]
History	Rashes, dark urine, abdominal pain	Respiratory distress	HTN, DM ,end stage renal disease, anosmia	Oropharyngeal SCC on treatment	Non especially unwell
CBC	Anaemia, leucocytosis +thrombocytopenia	Anaemia, leucocytosis	Anaemia, thrombocytopenia	Anaemia, thrombocytopenia	Mild anaemia
PS	Haemolytic picture+ RBC agglutination	Haemolytic picture	Haemolytic picture	Haemolytic picture+ RBC agglutination	Haemolytic picture
LFT	Deranged	Normal	Deranged	Normal	Deranged
KFT	NA	Normal	NA	Normal	Deranged
Coagulation profile PT (sec) INR D-dimer (ng/ml)	 22.9 1.75 -	 14.8 1.236 2728	 Normal Normal 15670	NA	NA
Inflammatory marker (IL-6, CRP, LDH)	Elevated	Elevated	Elevated	Elevated	NA
DCT	Positive	NA	Positive	Positive	Positive
Serology (positive)	IgG HAV, IgG EBV, IgG CMV and IgG *Mycoplasma*	IgM CMV and mycoplasma	NA	IgG EBV, IgG CMV, and IgM and IgG Mycoplasma	IgG Parvo B19 virus

[Table/Fig-6]: Autoimmune Haemolytic Anaemia (AIHA) comparison with available literature [4,16,17].

[16]. Venous Doppler ultrasound of upper extremities revealed clots in bilateral upper extremities. He was diagnosed as AIHA induced by cold agglutinin. Gowda V et al., studied haematological manifestation of nine infants suffering from congenital CMV infection [18]. Majority of infants had anaemia. Evidence of haemolysis were present in four (44%) patients in form of marked anisocytosis, poikilocytosis, schistocytosis, fragmented red cells on peripheral blood film examination and raised reticulocyte counts. Unconjugated hyperbilirubinemia was present in two infants. Thrombocytopenia was another striking feature. Almost half (44%) of the patients showed severe thrombocytopenia (platelets <50,000/mm^3). Bone marrow examination could be performed in three patients. It revealed erythroid hyperplasia and absence of megakaryocytes in one and paucity of erythroid and megakaryocytic cells in other two. Four of nine infants had conjugated hyperbilirubinemia and raised serum alanine transaminase values. This was similar to the case 3 in this study, with marked erythroblastopenia, megakaryocytopenia and trilineage dyspoiesis, which lead to death of the index case eventually.

CONCLUSION(S)

COVID-19 infection leads to varied spectrum of haematological manifestation, high index of suspicion and awareness about the same is of utmost importance for better management and saving the life of patient in such an ill understood and fast deteriorating multiorgan involving disease. Time based management, with high index of suspicion in the index cases is highly recommended.

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