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SEVERE THROMBOCYTOSIS IN PATIENTS WITH COVID-19 DISEASE: CASE REPORTS FROM A TERTIARY CARE CENTER IN NORTH INDIA

Clinical Hematology

Bhupendra Singh* Department of Clinical Hematology, King George's Medical University, Lucknow, India *Corresponding Author

Shailendra Prasad Verma Department of Clinical Hematology, King George's Medical University, Lucknow, India

Aparajita Singh Chauhan Department of Medicine, King George's Medical University, Lucknow, India

Himanshu Reddy Dandu Department of Medicine, King George's Medical University, Lucknow, India

Durga Prasad Verma Department of Medicine, King George's Medical University, Lucknow, India

ABSTRACT

Introduction: COVID-19 disease is reported to be associated with many hematological abnormalities including neutrophilia, leucopenia, thrombocytopenia, hemophagocytosis, thrombosis and disseminated intravascular coagulation. Thrombocytosis although seems to be common in view of underlying inflammation, it has not been reported in literature. **Methodology:** We reviewed 4 cases of COVID-19 who developed severe thrombocytosis. Clinical history, laboratory data, follow up and outcome was studied. **Results:** All patients had active symptoms in the form of extreme weakness and lethargy. Two of them had respiratory symptoms related to COVID pneumonitis sequelae. Three of them developed thrombocytosis post COVID while one patient developed it during active COVID-19 infection. Three patients had extreme thrombocytosis with large platelet clumps in peripheral smear. All except one, had elevated inflammatory markers. One patient died due to multiorgan failure. **Conclusions:** Thrombocytosis can be an easy marker of ongoing inflammation in COVID-19 disease during active COVID and post COVID recovery. These patients may need regular blood count monitoring and anticoagulation for longer duration in post COVID recovery period to prevent risk of venous thromboembolism.

KEYWORDS

Thrombocytosis, COVID-19, Thromboemblism

INTRODUCTION

Hematological abnormalities are frequently reported in patient with COVID-19 disease. Some of these abnormalities are seen during the active infection while others can be seen as post COVID effect. Neutrophilia, lymphopenia and thrombocytopenia are the most commonly identified abnormalities[1]. Mechanism for neutrophilia and lymphopenia in COVID-19 is not well known but thrombocytopenia can be explained by immune dysregulation, susceptibility mutations in SOCS1 and other attributable factors like molecular mimicry, cryptic antigenic expression and epitope spreading[2,3].[3]

Thrombocytosis is defined as a platelet count more than 450 x 10^9 /L while extreme thrombocytosis is defined as a platelet count of more than 1000 x 10^9/L[4,5]. Reactive thrombocytosis is a commonly encountered finding commonly seen in Iron deficiency anemia, asplenia, infectious diseases, cancers and in chronic inflammation[6]. Viral infection can cause both platelet destruction and platelet activation by different mechanisms. Viral infection causes an inflammatory reaction leading to release of platelet activating mediators and other pro- oxidative and pro- coagulant factors causing thrombocytosis [7]. COVID-19 related thrombocytosis has not been reported till date in available medical literature. Here, we report a case series of four cases who developed thrombocytosis during or post-COVID infection.

Case 1

This 38 year old female from Lucknow presented in march, 2020 with history of fever and bodyache for 3 days. She was diagnosed as COVID positive by RTPCR . She did not have any respiratory symptoms but got admitted in COVID care facility on 11/03/2020 as per current institutional protocol. Her hospital stay was uneventful and she became double negative on 21/03/2020. At the time of discharge her CBC was normal. After 3 weeks, she was called for plasma donation for a Covid-19 patient. Routine CBC was done as a prerequisite. Her hemoglobin (Hb) and total leucocyte count (TLC) was normal but peripheral smear showed large clumps of platelets suggestive of very high platelet count (**Figure-1**). She did not have any signs of thrombosis or bleeding but revealed about persistent weakness. In view of very high platelet counts she was counselled for low molecular weight heparin but she denied. Plasmapheresis was uneventful and she returned home. She consulted her physician after three weeks and a repeat CBC showed platelet count of 250 x10^9 /L , which was confirmed manually too. No other inflammatory markers were studied as it was not in the protocol at that time in our institute.

Case 2

An 84 year old male presented to the COVID-19 holding area in the 2nd week of December 2020 with moderate fever for 7 days and myalgia and difficulty in breathing for 3 days. He was detected COVID- 19 positive by RTPCR on nasopharyngeal swab (NPS) sample. The patient was a known case of hypertension, type 2 diabetes mellitus and chronic obstructive pulmonary disease (COPD). The patient was then shifted to COVID ICU as he was having multiple co-morbidities and not maintaining saturation on O2 mask. Standard institutional treatment protocol was followed and the patient tested negative on day 10 and in the subsequent sample by RTPCR, though difficulty in breathing persisted. He needed oxygen @ 2L/min at the time of discharge and he was referred to the pulmonary department for convalescence. There a CT scan of thorax was performed which suggested right sided pleural effusion with COVID related changes. During routine blood examination, consistent finding of neutrophilia and extreme thrombocytosis was found. Post COVID day-1 absolute neutrophil count (ANC) was 35000/mm3 and on day -10, ANC was 99X10^9/L while platelet count remained high at more than 1000 x 10^9 /L suggestive of extreme thrombocytosis **[Figure-2]**. Patient expired on D11, post discharge from COVID ICU due to multi-organ dysfunction syndrome and cardio-respiratory compromise while in non- COVID ICU setting.

Case-3

This 59 year male with co-morbidities of type-2 diabetes mellitus and bronchial asthma was diagnosed as mild COVID on 30/08/2020 and got admitted in a private COVID care setup. He remained on oxygen support 2-3 L/min without any need for invasive ventilation and became negative on September 19, 2020. He got readmitted for headache, weakness and exertional breathlessness on October 21, 2020 under pulmonary medicine and critical care. He also had multiple

petechiae over the upper and lower limbs. During this admission his CBC was Hb-128 gm/L, TLC-12.3X10^9/L and platelet count of 18x10^9/L. CT Thorax was suggestive of COVID pneumonitis. His CRP was elevated 52.1 mg/L(0-6). He was managed consevatively and his platelets increased to 75x10^9/L on 27/10/2020 following which he was discharged. During OPD follow-up his platelets increased to normal range.

The patient had persistence of symptoms and was evaluated by a different hospital on November 20, 2020. His two consecutive platelet counts were 475x10^9/L and 527x10^9/L. BCR-ABL and JAK-2V617F mutations were negative. His fibrinogen levels were > 517 mg/dl (200-400) and d-dimer was negative. Bone marrow was normocellular with normal megakaryocyte morphology. He was discharged from hospital on November 27,2020.

His current visit to our haematology OPD on December 7, 2020 was regarding persistent weakness, extreme tiredness and very high and persistent platelet count. Re-evaluation of his CBC revealed Hb-11.8 gm/dl, WBC-23X10^9/L and Platelet count of 935x10^9/L. Large platelet clumps were seen in peripheral smear examination with neutrophilia. He was found to have high CRP, high serum ferritin and LDH. In view of high platelets and raised inflammatory markers he was advised anticoagulation with LMWX and systemic steroid (Omnacortil 0.5 mg/kg BW). His CBC after 2 week revealed platelet count of 734x109/L. This case represents a case of persistent post COVID inflammation and reactive thrombocytosis. **Figure-3** shows platelet count trend during active COVID and post COVID follow up.

Case-4

A 35 year old male was diagnosed as a case of Diffuse large B Cell lymphoma (Germinal centre type) , Stage IIIB in October,2020. He was planned for VI cycles of R-CHOP chemotherapy on day care basis. During these chemotherapy cycles his platelet count was normal ranging from 180 x 10^9 /L to 260x 10^9/L. After two cycle of chemotherapy the patient was in clinical remission. Prior to the IIIrd cycle of R-CHOP chemotherapy (December 19, 2020) he presented to COVID holding area with moderate fever and breathlessness. Subsequently COVID- 19 test by RTPCR was positive and his X-Ray was suggestive of bilateral severe pneumonia. He was shifted to COVID-ICU due to severe breathlessness (SpO2-92% on 10 L/minute of Oxygen). Routine laboratory revealed leukocyte count ranging from 18.9 to 24.2 x 10^9/L and increased platelet count. Initially a platelet count of 300x 10^9 /L was seen further increasing to 625x 109/L on day 7 of admission and remained elevated for 1 week then gradually settled to normal. Inflammatory markers including CRP and IL-6 were 156.2 mg/L (0-6) and 66.2 pg/mL (<7) respectively. Serum ferritin was normal throughout hospital stay. At the time of writing this case the patient is in ICU at 2 litre/minute of oxygen support and still COVID positive on January 10, 2020. He received remdesivir, steroids and heparin prophylaxis along with other supportive measures during ICU stay.

Table -1 Summary including demographic details, clinical details and outcome of all four cases.

Platelet parameters and Inflammatory parameters were recorded at the time of detection of thrombocytosis for these patients. The values are tabulated in Table-2 below. Mean platelet volume, Platelet distribution width and Platelet large cell ratio was increased for all patients suggestive of reactive process. Inflammatory markers were also raised in three patients, in one patient markers were not done. These findings suggest reactive thrombocytosis in background of ongoing inflammation.

Table-1: Showing demographic details, clinical details and outcome of patients

Cases	Age (Years)	Sex	Symptoms	Duration of symptoms (Days)	Comorbidities	Complications	Diagnosis to development of thrombocytosis (days)	Time to recovery (Days)
Case-1	38	F	Fever Bodyache	3	None	None	30	21
Case-2	84	M	Fever Myalgia Respiratory distress	7	HTN Type-2 DM COPD	COVID Pneumonia Pleural effusion	15	Patient died after 2 weeks due to MOF
Case-3	59	M	Fever Myalgia Headache	5	Type-2 DM Bronchial Asthama	Mild pneumonitis	80	Persisted after 2 months follow up
Case-4	35	M	Fever Cough Dyspnoea	3	DLBCL, StageIIIB	Severe COCID pneumonia	10	14

Table-2: Showing platelet parameters and Inflammatory markers at the time of detection of thrombocytosis for all 4 cases.

Cases	Maximum Platelet count (X109/L)	Platelet Parameters			Inflammatory Parameters and D-Dimer			
		MPV(fL)	PDW(%)	PLCR(%)	IL-6(pg/ml)	CRP(mg/L)	Fibrinogen(mg/dl)	D-Dimer
Case-1	>1000*	11.1	20.4	33.4	ND	ND	ND	ND
Case-2	>1000*	11.6	18.1	24.6	136.2	98	510	1.5
Case-3	935	12.5	18.7	41.4	120	52.6	517	0.30
Case-4	625	11.9	21.9	37.7	66.2	156.2	451	0.72

CasesMaximum Platelet count (X10^9/L)Platelet Parameters Inflammatory Parameters and D-Dimer

* Large platelet clumps were seen in peripheral smear, MPV=Mean platelet volume, PDW=Platelet distribution width, PLCR= Platelet large cell ratio, IL-6 Interleukin-6, CRP=C-Reactive Protein , ND= Not done

DISCUSSION

COVID-19 disease, a global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2(SARS-CoV-2) is a highly infectious disease. Numerous studies regarding immunological and hematological patterns in patients with COVID-19 has been performed. Most of the study reported a common pattern of neutrophilia, lymphopenia, decreased counts of CD 3, CD 4 and CD8 T lymphocytes, increased inflammatory markers like C Reactive Protein (CRP), Serum Lactate dehydrogenase (LDH), serum ferritin, erythrocyte sedimentation rate (ESR) and interleukine 6 (IL-6)[8,9,10]. All these studies also reached to a common consensus that COVID- 19 is a hypercoagulable state with elevated levels of D - Dimer, fibrinogen and abnormalities of prothrombin time (PT) and activated partial thromboplastine time (APTT). Thromboembolic event, a commonly reported condition in COVID-19 cases is highly associated with increased risk of death. Mechanism behind these thromboembolic events is said to be caused by systemic inflammation and viral endothelitis[11,12].

Thrombocytopenia is not a rare finding in patients with COVID-19 disease. Many studies are available regarding COVID-19 related thrombocytopenia as an undisputable finding widely ranging from 5% to 72.5% in different reports. The mechanism behind thrombocytopenia is explained in a study by Si Zhang et al [13].

Thrombocytosis can be either primary or secondary due to reactive causes. Primary thrombocythaemia is noted in conditions like essential thrombocythaemia and other myeloproliferative neoplasms. Secondary thrombocytosis is more commonly encountered scenario in daily practice mainly associated with infection, chronic inflammation, iron deficiency anemia and malignancies [6]. Thrombopoetin (TPO) plays key role in regulation of platelet formation. It supports the

proliferation and differentiation of megakaryocytes.TPO is formed by liver and it is removed from the circulation by the platelet mass[14,15]. Thus regulation of the levels of TPO is an important step in platelet production.

Study in animal model suggests that regulation of TPO specially during inflammation, is finely articulated by the Interleukin-6 [16]. Administration of IL-6 to mice results in increased level of TPO m RNA steady-state levels in the liver, accompanied by increased TPO plasma levels. Finely this IL-6 administration increased the platelet count significantly. Another study to evaluate the influence of cGMP – dependent kinase I pathway on platelet formation also concluded that nonhematopoetic cells affects thrombopoiesis via elevated interleukin-6 production due to abnormal cGMP/cGKI signalling and ultimately leads to thrombocytosis [17]. Potential role of inteleukin 6 is also proven in reactive thrombocytosis even in patients of pulmonary tuberculosis [18]. An study by Charls W et al. suggested that elevated serum Interleukin-6 level was highly correlated with reactive thrombocytosis [19]. So, there is strong interaction between the interleukin-6, thrombopoetin and thrombopoesis.

Most of our patient had a fairly long duration of COVID-19 positivity or post COVID symptoms of disease related inflammation. Three of these patients had evidence of inflammation including raised IL-6, Serum LDH and CRP. This observation also raises a concern that these patients are having significant inflammation and a high risk of thrombotic and thromboembolic events. High platelet count can be considered as a easily available marker of inflammation and may be used as a maker to follow these patients for subsidence of inflammatory process. High platelet counts can be also considered for heparin prophylaxis/novel oral anticoagulant prophylaxis for the obvious reasons in view of case reports of sudden pulmonary embolism and death in the early post COVID period [20,21]. Close follow up of such patients is required.

CONCLUSIONS

COVID-19 infection is associated with a variety of hematological findings. Thrombocytosis is not reported in literature. We could find four cases of thrombocytosis during this COVID-Pandemic. Three patients developed it during post COVID recovery while one patient had it during active infection. This can be taken as a surrogate marker of ongoing inflammation and should prompt us to be more vigilant regarding the follow up of these patients and probably continuing heparin prophylaxis and steroid for a relatively longer time period in such patients.

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Author and Co-Author Contribution:
Dr Bhupendra Singh has collected the data and provided the concept and helped in write up preparation. Dr S.P.Verma has prepared the manuscript. Dr Aparajita and Dr Himanshu have helped in review of literature and discussion of this case. Dr Durga Prasad Verma has helped in editing and manuscript revision. The manuscript has been read and approved by all the authors.

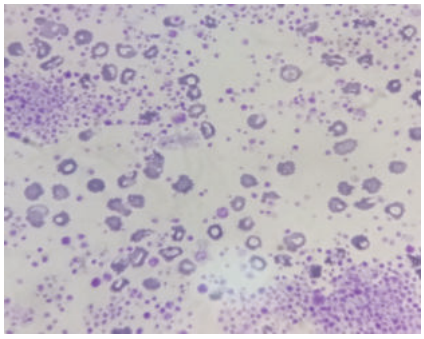

Figure-1. Peripheral smear showing marked thrombocytosis in case-1 (Leishman stain,100X)

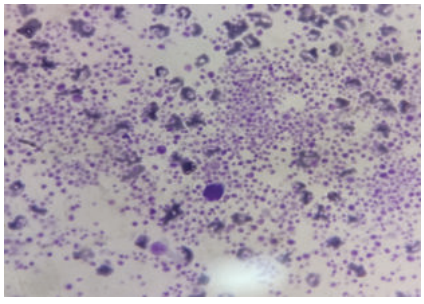

Figure-2. Peripheral smear showing marked thrombocytosis in case-2 (Leishman stain,100X)

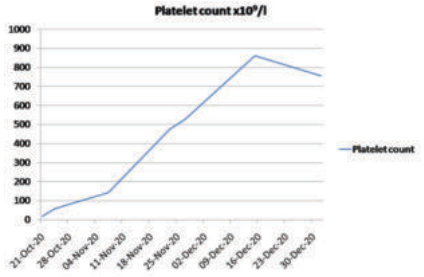

Figure-3. Shows platelet count trend during active COVID and post COVID follow up in case -3.

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