Case Report

"The Janus Face" of Thrombocytes in COVID-19

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ABSTRACT: A 55 year old patient of COVID-19, with no known comorbidities presented with fever, myalgia and headache and at presentation had leukopenia and thrombocytopenia, however did not have any bleeding manifestations. The patient's inflammatory markers including ferritin and C-reactive protein were elevated at admission. Later in the course of illness went on to develop severe thrombocytosis and leukocytosis. We discuss the course and outcome of illness in an unusual case of COVID-19 with severe and diametrically opposite haematological abnormalities.

KEYWORDS: *COVID-19, SARS-CoV-2, Thrombocytosis, Thrombocytopenia, Platelets, Hematology.*

Introduction

Late in 2019 there was the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in the Wuhan province of China [1].

The infection was brought to light by the increase in the incidence of atypical viral pneumonias in that particular region.

Soon over the next few months the disease spread to over 200 countries and was declared a global pandemic by the World Health Organization (WHO).

Coronavirus Disease 2019 (COVID-19) is now known to affect multiple systems including respiratory, neurological, immunological, haematological and other systems.

Thrombocytopenia is a well-known feature of this disease, with an incidence of approximately 20% [2].

Various mechanisms have been speculated to be causing this finding.

However, thrombocytosis is a rare finding in COVID-19 with isolated case reports [3].

Here we describe a case of COVID-19 who initially developed thrombocytopenia but during the course in hospital went on to develop severe thrombocytosis.

Case Report

A 55-year-old gentleman, a driver by profession, without any known comorbidities, presented to a COVID-19 clinic in New Delhi with fever, myalgia and headache of 5 days duration in August 2020.

He did not have any history of international travel or contact with a COVID-19 patient.

During evaluation for his symptoms a nasopharyngeal swab was taken and SARS-CoV-2 RT PCR was done on 2nd August 2020, which was positive.

All tests were done at Sardar Vallabh Bhai Patel (SVBP) COVID hospital, New Delhi and he was admitted to this hospital the same day.

On admission he was afebrile, vitals stable and he was maintaining saturation at room air. Chest auscultation revealed bilateral crackles.

Laboratory results on admission showed thrombocytopenia with a platelet count of 45,000 cells/μL and total leucocyte count of 1300 cells/μL showing lymphocyte dominance (59%) and relatively neutropenia (30%).

He underwent serial hemograms to look for monitoring the trend of haematological parameters.

During his hospital stay he was administered intravenous antibiotics (Inj Ceftriaxone 1gm IV BD, Inj Levofloxacin 750mg IV OD and Inj Piperacillin+Tazobactam 4.5gm IV QID), Inj Enoxaparin (40mg SC OD) in prophylactic doses, tapering doses of dexamethasone (6mg IV BD) and antiviral therapy in the form of Remdesivir (200mg IV OD Day1→100mg IV OD Day 2-5).

Subsequent laboratory studies showed the patient's platelet count continuing to decline to a nadir of 35,000/μL, on day 2 of admission (Table 1), and a peripheral blood smear (PBS) taken on the 2nd day of admission showed leukopenia and reduced platelets.

The PBS showed no platelet aggregation or giant platelets.

Chest radiographs revealed irregular faint opacities in right upper and middle zones (Figures 3, 4). High-resolution CT (HRCT) of the chest revealed multiple ground glass opacities and areas of consolidations bilaterally.

Abdominal pelvic sonography did not show any abnormality, without organomegaly and

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other viral markers including NS1Ag, HCV-Ab, HBs-Ag, IgM HBc and HIV were unremarkable.

Other laboratory parameters like the renal function tests, liver function tests and serum electrolytes were essentially normal.

The inflammatory markers including C-reactive protein, interleukin 6 and ferritin were at the peak at admission and continued to decline during the period of hospitalization (Table 1).

Table 1. Variation of Laboratory parameters.

Day of admission	D1	D5	D10	D16	Range
Hemoglobin (Hb)	14.2	13.2	12	13.2	13.5-18.0gm/dl
Total Leucocyte count (TLC)	1300	1500	19900	22,400	4000-10000/μL
Platelets	45	3.5	16	3.61	1.50-4.00 x10^5/μL
CRP	>90	76	8	1.06	<5mg/L
IL-6	82.54	8.15			<7pg/mL
Ferritin	1528.8	1108	501	370.1	25-350ng/ml
D-dimer		1.04	0.73	350	<0.5mg/L

On day 3 of admission patients platelet counts started to rise along with an increase in TLC.

There was a serial increase in both these parameters during the subsequent days.

The platelet count reached to a maximum of 13.27 x 10^5 cells/μL on day 12 of admission, when the patient was started on aspirin at a dose of 350mg/day and started to decline gradually the following days.

PBS during these days showed thrombocytosis with neutrophilic leukocytosis (31,000 cells/μL, neutrophils 83%) and no evidence of atypical cells, left shift, sepsis, giant platelets, clumping of platelets or any other morphological abnormality (Figure 1).

A leucocyte alkaline phosphatase (LAP) score was obtained which attributed the leukocytosis to a leukemoid reaction.

A procalcitonin level of less than 0.1 on day 12 of the illness ruled out any active bacterial infection.

Given the hematopoetic abnormalities, a bone marrow aspiration and biopsy were considered.

However, the improvement of patient profile during the subsequent days along with normalization of the haematological parameters entailed that a bone marrow biopsy was no longer necessary (Figure 2).

The patient was asymptomatic and his haematological and biochemical parameters were within acceptable levels, he was discharged on 21 August 2020.

The patient has given a written informed consent regarding the publication of this data.

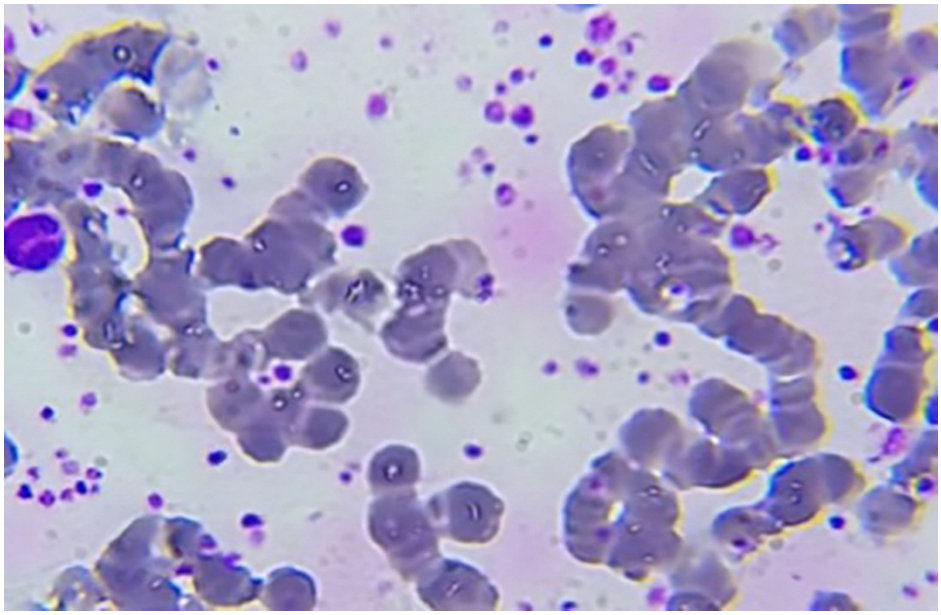

Figure 1. Peripheral blood smear obtained on day 12 of illness shows normocytic normochromic red cells. Moderate thrombocytosis is noted with marked anisocytosis in platelets. Giant platelets are also noted. (May-Grünwald-Giemsa, 400×).

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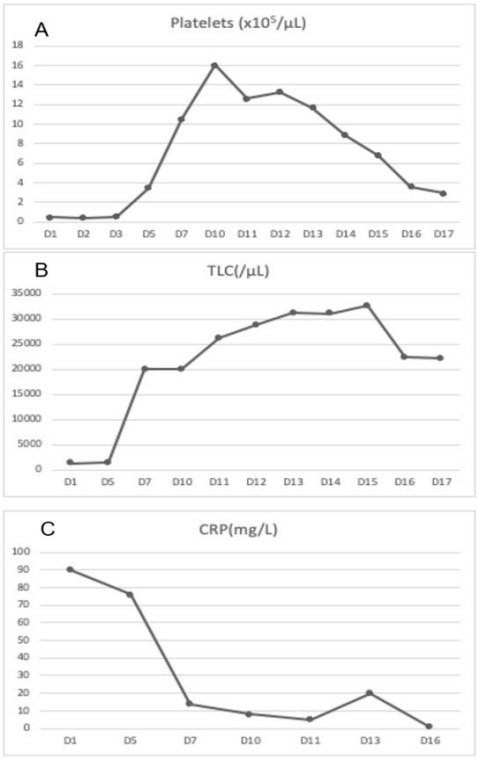

Figure 2. X axis represents day of illness, Y axis represents the count. A. Line graph showing temporal trend of platelets. B. Line graph showing temporal trend of TLC (Total Leukocyte Count). C. Line graph showing temporal trend of CRP (C reactive protein).

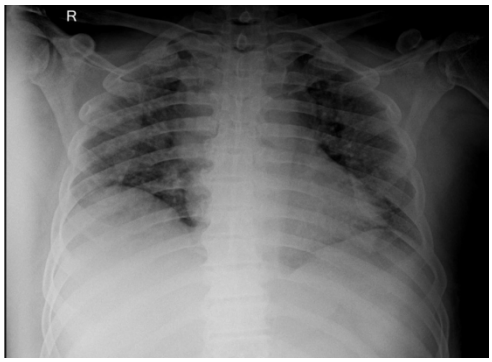

Figure 3. Chest X ray posteroanterior view, day 13 of evolution.

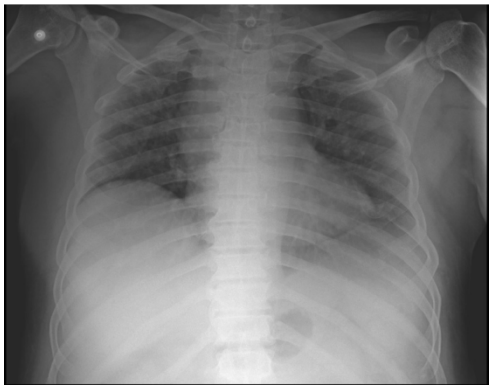

Figure 4. Chest X ray posteroanterior view, day 21 of evolution.

Discussion

In this case report, we presented a case of COVID-19 infection who reported with symptoms of fever, myalgia and headache.

Evaluation at presentation revealed leukopenia and thrombocytopenia, however, the patient had no bleeding manifestation.

The thrombocytopenia and leukopenia were transient and over the course of admission the patient developed severe thrombocytosis and leucocytosis.

Thrombocytopenia is a known laboratory feature of this disease with an incidence of approximately 20% and having a strong association with the severity of the disease [2].

Various mechanisms resulting in leukocytopenia and thrombocytopenia in COVID-19 include decreased platelet production due to the cytokine storm and invasion of bone marrow stromal cells, autoantibodies and immune complexes mediated increased platelet destruction and platelet consumption by microthrombi.

The associated leucopenia could be a result of cytopenia associated in viral infection, followed by leucocytosis, which may be reactive or as a result of hyperinflammation, or due to steroid induced demarginating of leucocytes and less likely due to secondary infection since the illness ran a self-limiting course.

Viral illnesses per se cause a variety of hematological manifestations, namely pancytopenia, aplastic anaemia, hemophagocytic lymphohistiocytosis (HLH), acute myeloid leukemia (AML) and primary myelodysplastic syndrome.

Viruses like Epsitein Barr Virus (EBV), Cytomegalovirus (CMV), Varicella Zoster Virus (VZV), Human Herpes Virus (HHV), Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), Parvovirus B-19, Dengue Virus and Hepatitis C Virus (HCV) are notorious for causing hematological abnormalities in patients.

Four different pathological reasons have been implicated for this, namely: direct viral infection of Hematopoietic stem and progenitor cells (HSPCs), viral recognition by HSPCs, and indirect effects on HSPCs consecutive the release of inflammatory mediators, and the role of the bone marrow microenvironment on haematopoiesis upon virus infection.

Inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-10, TNFα, GM-CSF, TGFβ, CCL3 (MIP-1α), CCL4 (MIP-1β), CXCL10 (IP-10), and type I IFNs have been implicated in causing most of the damage in proliferative disorders.

However, the complex interactions between the bone marrow environment, inflammatory mediators, viruses and HSPCs, are still grossly unrecognized [4].

There have been rare cases of thrombocytosis in this disease.

Thrombocytosis can be primarily due to hematopoietic malignancy like polycythemia

Vera, primary myelofibrosis, essential thrombocytopenia or chronic myelogenous leukemia.

These causes were excluded on the basis of an essentially normal hemogram with no other constitutional symptoms and resolution of thrombocytosis.

The course of infection and thrombocytosis were strongly correlated, considering gradual resolution of thrombocytosis with improvement in symptoms over a span of 20-22 days (the median length of disease noted in hospitalized patients).

The pathogenesis of thrombocytosis in any infection primarily involves increasing levels of IL-6 which stimulates megakaryopoiesis directly and indirectly through increased TPO production by the liver.

In the mentioned case, IL-6 levels of the patient on Day-7 of infection were elevated to 4 times above the normal.

The disease course has three phases namely the early infection, pulmonary and hyperinflammation [5].

The initial thrombocytopenia in this patient can be attributed to the stage 1 and 2 of the disease, due to increased consumption of platelets in the pulmonary microthrombi.

The subsequent thrombocytosis can be a late response to hyperinflammatory state.

Thrombocytosis in this case was by itself self-limiting.

However, in view of severe thrombocytosis and COVID-19 being a procoagulant state the patients was started on Tablet Aspirin.

The clinical course in this case was uneventful, however this shows that hyperinflammation could be responsible for late thrombotic events in COVID-19 survivors.

This paper highlights the atypical laboratory manifestation of COVID-19 in form of thrombocytosis.

Till now no definite pathogenesis has be linked to this manifestation, primarily because not enough cases have presented with these features.

It is therefore important to look for this atypical manifestation in both hospitalised patients and survivors to better understand the risk of increased thrombotic events in COVID-19.

Conflict of interests

None to declare.

References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y. Early transmission dynamics in Wuhan China of novel coronavirus-infected pneumonia. N Engl J Med, 2020, 382:1199-207.
2. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta, 2020, 506:145-148.
3. Sadr S, Seyedalinaghi SA, Ghiasvand F, Hassan Nezhad M, Javadian N, Hossienzade R. Isolated severe thrombocytopenia in a patient with COVID-19: A case report. IDCases, 2020, 21:e00820.
4. Pascutti MF, Erkelens MN, Nolte MA. Impact of viral infections on hematopoiesis: From beneficial to detrimental effects on bone marrow output. Frontiers in Immunology, 2016, 7:364.
5. Romagnoli S, Peris A, de Gaudio AR, Geppetti P. SARS-CoV-2 and COVID-19: From the bench to the bedside. Physiol Rev, 2020, 100(4):1455-1466.

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