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An unusual leukemoid reaction in COVID – 19 patients , simulating as Chronic Myeloid Leukemia: A Case Series

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Abstract : The hematological alterations are one of the key features that aided the diagnosis and prognostic evaluation in patients of COVID – 19 infection. The reports that appeared in literature were mostly describing the hematological alterations of leukocytosis,lymphopenia, thrombocytopenia and deranged cellular ratios in patients of COVID – 19 infection. The present case report describes two unusual patients of COVID – 19 infection with myeloid leukaemoid reactions which were unique for their cell counts and cell types. These myeloid – leukaemoid reactions were having the total leukocyte counts and differential leukocyte counts close to the one seen in patients of chronic myeloid leukemia (CML).However, these chronic myeloid leukaemia like leukamoid reaction receded as the patients were put to appropriate therapy with improvement in their clinical conditions.

Keywords : COVID – 19 infection , myeloid-leukaemoid reaction , chronic myeloid leukemia

INTRODUCTION

COVID – 19 is complicated by the diversity for its presentation, though it primarily manifests as a respiratory infection. By now it is recorded as a systemic disease involving multiple systems such as gastrointestinal, neurological, cardiovascular, immune and haemopoietic. The course of COVID – 19 is marked by many unusual and unexpected findings in the patients, which are pertaining to hematology. Disseminated Intravascular Coagulopathy (DIC) and several other complications with non-specific symptoms related to hematology have also been reported which are pathogenetically linked to cytokine storm [1,2].Marked increased levels of interleukin – 6 , interleukin – 2 , interleukin – 7, granulocyte colony stimulating factor (GCSF) , interferon – gamma (IF- ɣ) , MCP – 1 , MIP – 1 and tumournecrosingfactor (TNF-ά) are responsible for haematopathological events in the patients suffering from COVID -19[3].

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Amongst the diverse hematological manifestations lymphopenia , increased leukocyte count, abnormal lymphocyte morphology, alterations to hematological indices (platelet/lymphocyte ratio) , leukoerythroblastic reactions, plasmacytoid lymphocytosis, circulating apoptotic leukocytes and thrombocytopenias are a few which are reported in literature in the patients suffering fromCOVID – 19 infection[4,5,6].

Here is a report of two cases of the patients suffering from COVID – 19 with unexpected and unusual hematological manifestations of marked leukamoid reaction simulating the chronic myeloid leukaemia (CML) in the patients who had normal hematology profile for leukocyte counts and morphology on previous instances of checkups. This is the report generated from a dedicated COVID – 19 hospital with a tertiary care facility.

CASE REPORTS

Case 1

A 60 years old man, reported to medicine OPD with complaints of breathlessness and fever for past 4 days . The patient was later evaluated by a consultant in dedicated COVID – 19 OPD and was advised admission for further clinical evaluation.The history revealed his contact with COVID – 19 positive patients. He gave a history of travel. He was a known case of systemic hypertension for past years and was on medication. He had a negative history for diabetes mellitus and other respiratory disease such as pulmonary tuberculosis and bronchial asthma.

On physical examination, he appeared moderately built but presented with obvious breathlessness, suspicious of Acute respiratory failure. Vitals were stable except of respiratory rate. He had no organomegaly.Nasal swab and throat swab was collected from patient and were subjected for investigation of rapid COVID – 19 antigen test and RT-PCR which was reported positive for COVID – 19 infection (corona virus).Meanwhile, patient underwent the CT chest. It showed bilateral homogenous patchy opacities in all lung fields which had CORAD scored 19 out of 25. The basal biochemistry investigation for KFT and LFT were within normal limits. The investigations carried out on a urine sample were negative for the presence of proteins and sugar.

The ferritin levels were 298 microgram/deciliter.His hematological investigations were also sent on the day of his admission. Total WBC count was 68,700 cells/cumm and hemoglobin was 8.4 gm/dl. Hematocrit was reduced (27%) and RDW was 21.2%.The other hematological indices of MCV,MCH and MCHC were in normal limit. The platelets were reduced (1,46, 000 cells/cumm) while , mean platelet volume (MPV) was within limits. The differential counts showed shift to left with many immature granulocytes and nucleated red blood cells. The last differential count was like –Myeloblasts – 00%, Promyelocyte – 06% ,Myelocyte – 17% ,Metamyelocyte – 18%, Neutrophils and band forms – 42%, Eosinophils and its precursors – 05%, Basophils – 03%, Lymphocytes – 05% , Monocytes – 04%

This hematological profile was highly suspected of Chronic Myeloid Leukaemia (CML). However, the diagnosis offered was on myeloid-leukamoid reaction (Figure 1) and bone

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marrowexamination was advised.The bone marrow smears of the case showed a little change for Myeloid:Erythroid ratio = 6:1 with myeloblast count as 03%.The erythropoiesis was within normal limits, so was the thrombocytopoiesis. The patient was put under the treatment of COVID – 19 protocols. The similar blood picture lasted on one subsequent occasion collected after two days. The total leukocyte count started falling after the 5th day of treatment, so also the presence of immature myeloid series in peripheral blood .After all the workups and proper treatment, his hematological parameters improved and started reaching to the normal.Further plan to evaluate the patient for ABL – BCR translocation was aborted.

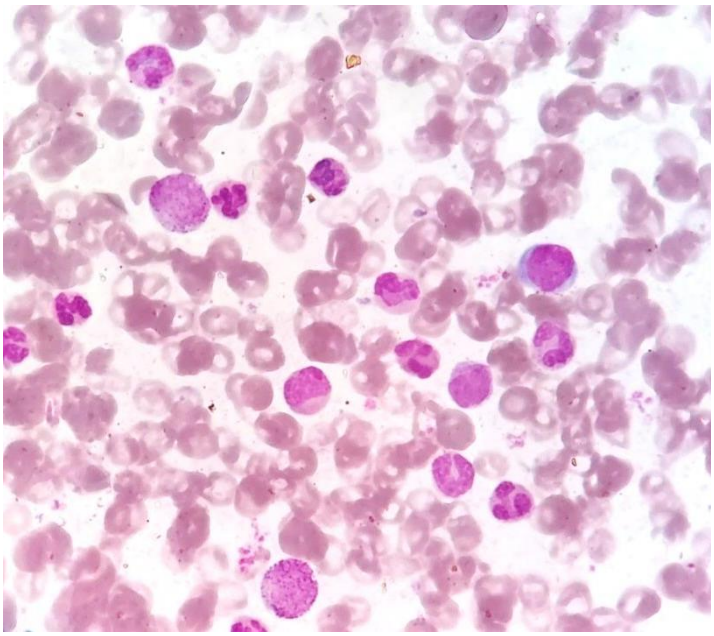

Figure 1: Myeloid leukaemoid reaction (Case 1) : Peripheral blood smear shows immature myeloid cells (promyelocyte and myelocyte) and band cells .(Leishman stain , 100x)

Case 2

A 31 year old woman presented with unrelated symptoms of COVID – 19 in patients department of Gynecology. She complained of heavy bleeding per vagina with a history of passing clots and abdominal discomfort. As per the hospital protocol, she was referred to COVID – 19 screening for the test of RTPCR on a throat and nasal swab, on the same day of admission. Apart from these presenting symptoms she had no other systemic manifestations such as cough, breathlessness or fever.Her personal history was insignificant.The bleeding per vagina was a first time episode as she has reported.She gave no history of blood transfusion. Her obstetric history was P1 L1 with a previous lower segment caesarian section. Clinical examination revealed the presences of mild splenomegaly and hepatomegaly. The abdomen was soft and no complaints in bowel and bladder habits were reported. She underwent the USG of abdomen which recorded the mild splenomegaly and hepatomegaly with no other visceral organomegaly. The liver showed the suspected lesion of hemangioma in segment IV b of the liver. There was a small hemangioma in pelvis with a minimal collection in Pouch of Douglas.The chest X-ray revealed no evidence of pneumonitis. Her vitals were stable with a blood pressure of 110/70 mm of hg.

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The hematological investigations were performed on the same day of her admission showed certain abnormal observations. The total leukocyte count was 44,700cells per cumm with MCV normal, MCH normal, MCHC reduced and RDW normal. The cell counter and peripheral smear showed shift to left with immature granulocytes. The differential leukocyte count was –Myeloblasts – 00%, Promyelocyte – 03% ,Myelocyte –07% ,Metamyelocyte – 19%, Neutrophils and band forms – 44%, Eosinophils - 06%, Basophils – 00%, Lymphocytes – 18% and Monocytes – 03% (Figure 2) .A diagnosis of myeloid-leukaemoid reaction was offered. The Bone marrow examination was not performed.

Biochemistry of the blood reported, normal KFT and normal LFT with normal levels of Ferritin. However, CRP (2.9mg/L)and D-dimer (1.21 mcg/ml) was a little raised. The LDH level was found to be raised upto 1446 U/L . The values of sodium was in normal limits but potassium appeared to be reduced (2.5mEq/L). She also had normal blood sugar.The investigation carried out on a urine sample was negative for the presence of proteins and sugar.Meanwhile, her RTPCR on throat and nasal swabs was reported positive.

She was appropriately treated for COVID – 19 as well as was treated for her bleeding per vagina, by medication. The clinical and laboratory improvements in her condition was observed after 5 days of medication. At discharge, she was hematologically and biochemically reported to have parameters within normal ranges.Her bleeding per vagina was attributed as the limited phenomenon of DIC in a patient with hepatic hemangioma complicated by COVID – 19 patient with a support of increased values of acute reactant proteins of CRP and D-dimer. As the patient showed improvement in hematological parameters , plan to evaluate patient for ABL – BCR translocation was not considered.

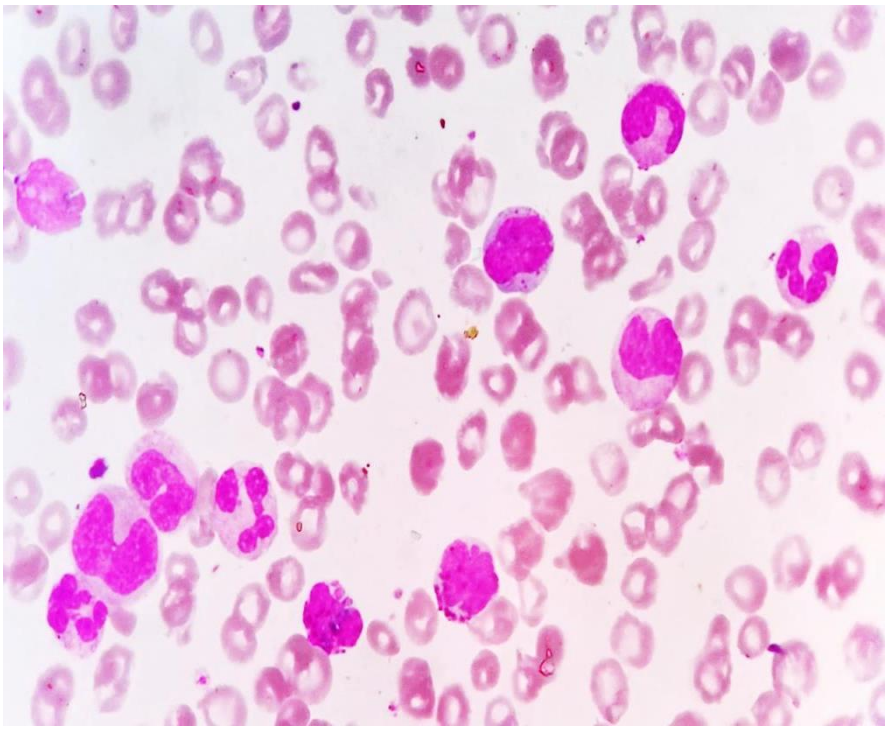

Figure 2 : Myeloid leukaemoid reaction (Case 2) : Peripheral blood smear shows immature myeloid cells (metamyelocyte) and band cells . (Leishman stain , 100x)

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DISCUSSION

The corona viruses struck on population across globe frequently in last decade which caused fatal respiratory disease. The recent pandemic of COVID – 19 has been perceived as major threat to public health worldwide. The initial clinical manifestations for the infection of COVID – 19 remained nonspecific to specific for their multi-systemic involvement. However, its primary clinical presentation by now has been known to involve upper respiratory tract, lower respiratory tract and manifests as severe acute respiratory syndrome (ARDS)[1].

The testing for antigen – antibody against COVID – 19 and the PCR for viral protein collected of nasal swabs and throat swabs remained diagnostic mainstay. However, the abnormalities in the biochemical values and hematological tests have proven potentially to indicate the diagnosis and clinical course of disease enabling appropriate treatment interventions to limit the fatality of COVID – 19 infections. The hematological alterations in COVID – 19 infection have been reported in the literature for its unusualness[7].

A review of Toledo et al.[4] for hematological impact in COVID – 19 infection have an interesting fact file. This review had quoted the findings in hematologic parameters from various studies with in constant dynamics of differential counts and total leukocyte counts.
The commonest hematological findings quoted from various studies by Toledo et al.[4] was of lymphocytopenia , neutrophilia , eosinopenia, mild thrombocytopenia and infrequent thrombocytosis. However, one of the meta analysis paper quoted in the review of Toledo et al. has found, leukocytosis of greater severity with unfavourable outcome of infection.The same review have also reported that a decrease in lymphocyte/total leukocyte count ratio has been associated with severe disease and fatal outcome. The changes in total leukocyte count varied from first day of the disease posteriorly to 7^{th} to 14^{th} day of infection was another interesting hematological alterations.Most of these hematological alterations are attributed to systemic inflammatory process largely mediated by cytokine productions [4].

The another critical review of hematogical findings and complications by Terpos et al.[3]reported several studies that neutrophil: lymphocyte ratio and platelet : lymphocyte ratio to have prognostic value in determining severity of COVID – 19 infection[3].

Zhao et al.[1]observed an elevated leukocyte count in 52 patients with COVID – 19. The rise of the total leukocyte count was more frequent and older, was another observation in the same study [1].

Mitra et al. [5]reported a eukoerythroblastic reaction in a patient with COVID – 19 infection. In their case the peripheral examination showed the leukocytosis (14.1 x 100 microlitre) with a left shift of neutrophilic cells. There was a mild monocytosis along with persistent lymphopenia. This neutophilia with left shifted myeloid cells including occasional myelocytes and rare promyelocytes was another unusual finding.This case reports of Mitra et al.[5]is much similar to the two cases which are reported presently for their peripheral blood findings except for the presence of erythroblasts in the smear.

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Yun et al.[8]in their study observed that the patients of COVID – 19 showed decrease lymphocyte count and decrease eosinophillic counts. However, none of the above studies have reported leukamoid reaction in the patients of COVID – 19. The presently reported two cases show a transient myeloid leukamoid reaction simulating a peripheral smear of chronic myeloid leukaemia. The total leukocyte count and differential count both in these two patients has given a fallacious impression of chronic myeloid leukaemia. However, the fall in the total leukocyte count and gradual disappearance of immature myeloid series cells over a week's time in these two cases was an unusual finding. Such a chronic myeloid leukaemia like peripheral blood picture has yet not been reported to the best of our knowledge.[8]

SA et al.[9]reported an unusual reaction in a COVID – 19 patient who was 76 years old male. The patient had total white blood cells count of 96.6 x 10^9 per litre on the 5^{th} day of the diagnosis of COVID – 19 infection, it was diagnosed as leukamoidrecation with left shift with presence of myelocytes and metamyelocytes. JAK – 2 mutation was negative and Leukocyte AlkalinePhosphatase score was less than 18 which ruled out myeloproliferative disease. The patient expired on the 5^{th} day due to Acute Respiratory Disease Syndrome (ARDS). This case report assumes the importance for a chronic myeloid leukaemia like leukamoid reaction has been reported much similar to the presently reported cases. However, unlike SA et al.'s[9]report, presently reported two cases of COVID – 19 with chronic myeloid leukaemia like leukamoid reaction survived.

Lee et al. and Margolskee et al.[10]attributed this leukoerythroblastosis in the patients of COVID – 19 infections to the cytokine storm with multi system inflammatory syndromes.
The reports of the present two cases , for their hematological alterations, pertaining to the leukocytes is a flag of caution over reporting of these patients as a case of chronic myeloid leukaemia. Therefore, the laboratory studies for exclusion of JAK – 2mutations and ABL – BCR translocations should be performed in exclusion of chronic myeloid leukaemia being complicated by COVID – 19 infection[7,11].Chronic myeloid leukaemia and chronic lymphocytic leukaemia complicated by COVID – 19 infections has also been observed and reported in few other studies[7,11 -13]. Few more related studies were reviewed[14-16].

The presently reported cases, are unusual for hematological alterations where the total leukocyte count were so high reaching to the chronic myeloid leukaemia for its ranges. The differential counts too had shown the shift to left uptopromyelocytes which is another confusing morphology for chronic myeloid leukaemia.

The COVID – 19 infection as many authors have reported shows lymphopenia , decrease of lymphocytes to total leukocyte ratios , thrombocytopenias , abnormal platelet : lymphocyte ratio and leukocytosis [3,4].However, these 2 cases were entirely different for their hematological alterations. Has the status of COVID– 19 being not known in this case , these cases would have branded as chronic myeloid leukaemia for the diagnosis.

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CONCLUSION

These case reports brought out three hematological highlights for learning – i) COVID– 19 may be associated with a myeloid – leukamoid reaction simulating morphologically as chronic myeloid leukaemia,ii) improvements of clinical parameters upon treatment in COVID – 19 patients recedes the count, iii) persistent leukamoid reaction with shift uptopromyelocyte should prompt pathologist to JAK – 2 and BCR- ABL to exclude myeloproliferative disease co existing with COVID – 19 infection.

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