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Original article

Leukoerythroblastosis – An unsusal presentation of COVID 19 infection

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ABSTRACT

Objectives: Although several peripheral blood abnormalities have been reported in COVID 19,Leukoerythroblastosis is an unusual finding. We report 33 COVID19 cases presenting with leukoerythroblastosis. We intend to describe its incidence in this novel viral infection and correlate it with the clinical outcome.
Methods: It is a Prospective study done at a Level 3 COVID 19 hospital of LUCKNOW, INDIA. Hematologic test records of day 1 of admission of COVID 19 cases admitted from 20th August 2020 to 30th September 2020 were reviewed. Peripheral blood smear examination was performed on test results that were flagged for abnormalities. Leukoerythroblastosis was reported when the smears showed presence of granulocyte left shift and nucleated red blood cells. Follow up smears were examined on Day 7. The findings were correlated with the clinical outcome.
Results: Out of 274 slides reviewed, 33 (12%) showed a leukoerythroblastic picture on day 1 of admission. Follow up smears on day 7 were available in 76% (25/33) cases. The follow up smears showed improvement in 13 cases, worsening in 9 cases and no changes in 3 cases. There were total 19 (58%) deaths. 12 patients (36%) recovered and 2 patients (6%) were shifted to other hospitals whose further follow up was not available.
Conclusions: Leukoerythroblastosis is an unusual presentation of COVID 19. Although rare, this peripheral blood abnormality can provide insight into the underlying pathophysiologic processes. Furthermore, it seems to be an adverse prognostic factor, so examination of follow up smears may help clinicians and intensivists to make prompt management decisions.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic disease caused by a novel coronavirus named "Severe Acute Respiratory Syndrome Corona virus-2 (SARS-CoV-2)"with surface spike protein binding to the human angiotensin-converting enzyme 2 (ACE2) receptor.[1,2] SARS-CoV-2 infections ranges from asymptomatic carriers to mild respiratory symptoms and fatal acute respiratory distress syndrome. The virus causes T-cell immune dysregulation, especially in immunocompromised patients, resulting in monocyte/macrophage activation, uncontrolled cytokine release, and multiorgan dysfunction.[3] The most common hematological findings in COVID 19 infection as reported by several studies include lymphopenia, neutrophilia, eosinopenia, thrombocytopenia and occasionally, thrombocytosis.[4–11] In this study, we report unusual finding of leukoerythroblastosis on peripheral blood smear examination of patients infected with COVID 19 and correlate this finding with the clinical outcome.

2. Materials and methods

It is a Prospective study done at the Emergency Laboratory of dedicated COVID 19 hospital of Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow which provides level 3 care to COVID 19 patients. This work was done after approval of institutional ethics committee and subjects were enrolled after obtaining their written informed consent. The study subjects include cases admitted between August 20, 2020 to September 30, 2020 after a positive SARS CoV2 RNA detection on nasal/nasopharyngeal swab on Reverse Transcriptase polymerase chain reaction (RTPCR) assay. The list of all patients tested positive for COVID 19 and admitted to our hospital was obtained on daily basis. Investigation records of day 1 of admission of these positive cases were reviewed for hematologic tests performed. Complete blood cell counts (CBCs) were performed on Abbott Alinity hq which provides CBC with 6 – part White blood cells (WBC) differential counts. Peripheral blood smear examination was performed on test results that were flagged for abnormalities

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as per slide review criteria followed in our laboratory. The blood smears were stained with Leishman stain. A total of 418 patients were admitted with COVID-19 infection during the above mentioned period of the study, out of which 274 patients had CBC abnormalities and their smears were examined. A leukoerythroblastic blood picture was reported in cases in which the smears showed presence of granulocyte left shift and nucleated red blood cells. Granulocyte left shift was defined as either[12]

- peripheral blood showing increased neutrophil band forms (>10% of WBC) by manual differential cell count or
- increased number or percent of immature granulocytes detected by automated cell analyzer, which typically represents promyelocytes, myelocytes, and metamyelocytes or
- a flag for left shift.

Based on the document on CLINICAL MANAGEMENT PROTOCOL: COVID-19 by Ministry of Health and Family Welfare, Government of India, we categorized the patients with leukoerythroblastic blood picture into mild, moderate and severe.[13]

Follow up smears of these patients were examined on Day 7 after admission.

3. Results

Out of 274 slides reported, 33 (12%) showed a leukoerythroblastic picture on day 1. These 33 COVID-19 cases included 21 men and 12 women, with an age range of 18–87 years (Median age 49 years).

The patients presented predominantly with shortness of breath and fever followed by cough, bodyache, tiredness, weakness and altered sensorium (Table 1).

Based on clinical severity and assessment parameters,[13] patients were categorized as follows. Most cases belonged to severe category (Table 2).

CBC revealed anemia in most patients followed by neutrophilic leukocytosis and thrombocytopenia. Absolute Neutrophilia and Absolute Lymphopenia were among other common findings. Absolute

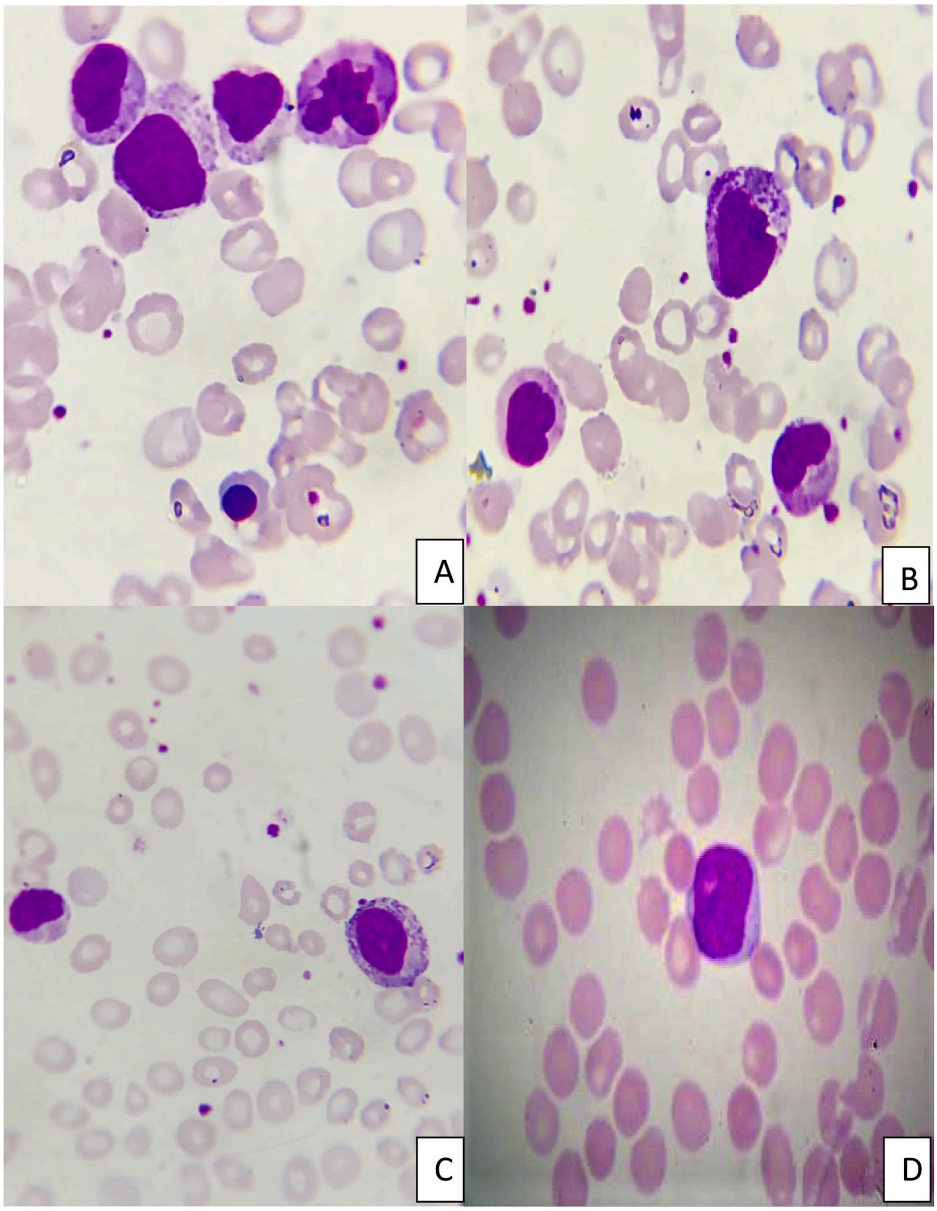

Image 1. Review of the peripheral smears of 33 patients at 1000× magnification showing - A Nucleated Red Blood Cell along with a left shifted myeloid series with myelocyte and metamyelocyte (A); promyelocytes and metamyelocytes (B & C); Occasional Blast with prominent nucleoli and immature fine chromatin (D).

Table 1
Clinical presentations on admission.

Clinical presentations	Shortness of breath	Fever	Cough	Bodyache	Tiredness, Weakness and altered sensorium
(n = 33)	64% (n = 21)	56% (n = 19)	30% (n = 10)	12% (n = 4)	9% (n = 3)

Table 2
Clinical severity on admission.

Clinical severity	Mild	Moderate	Severe
(n = 33)	30% (n = 10)	3% (n = 1)	67% (n = 22)

monocyte count was high in 10 patients. Absolute eosinophil count was normal in all patients (Table 3).

Morphologic findings on peripheral smear examination of all 33 cases revealed a leukoerythroblastic blood picture. 70% (23/33) of these cases showed left shift up to metamyelocyte/myelocyte stage, 15% of cases (5/33) showed left shift up to promyelocytes, 12% (4/33) showed presence of blasts and 3% (1/33) showed left shift up to band form stage. NRBC/100 WBCs varied from 1% to 10% in these cases (See Image 1). None of these patients had a history of myeloid neoplasms and none had received chemotherapy or growth factors in the recent past.

Most patients had comorbidities at presentation, which included hypertension in 24% (8/33) cases, type 2 Diabetes Mellitus in 21% (7/33) cases, hypothyroidism 9% (3/33) cases, pregnancy 9% (3/33) cases and chronic kidney disease 6% (2/33) cases.

CBC and follow up smears on day 7 were available in 76% (25/33) cases. Out of these, the peripheral smear findings on day 7 showed improvement in 12 cases, worsening in 10 cases and no changes in 3 cases (Table 4).

There were total 19 (58%) deaths. 12 patients (36%) recovered and were discharged and 2 patients (6%) were shifted to other hospitals whose clinical outcome was not known. 13 patients (39.4%) required mechanical ventilation.

4. Discussion

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus.[1] It is a global pandemic disease caused by the "Severe Acute Respiratory Syndrome Corona virus-2 (SARS-CoV-2)" with surface spike protein binding to the human angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in the lung (type 2 alveolar cells), heart, intestinal epithelium, vascular endothelium, and kidneys causing multi-organ dysfunction. The median incubation period is 4–5 days and 97.5% of patients will have symptoms within 11.5 days.[2] COVID-19 is highly transmissible among humans. Most of the symptomatic patients have mild flu-like features but a significant subset develops bronchopneumonia, which clinically is the acute respiratory distress syndrome (ARDS) leading to significant morbidity and mortality.[14] The fatality rates of COVID-19 are highest amongst older patients with concomitant comorbidities and/or patients who are immunosuppressed.[15]

In our cohort of 33 cases, most common clinical symptoms were shortness of breath and fever followed by cough, bodyache, tiredness, weakness and altered sensorium. This was in accordance with the studies of Rodriguez-Morales A.J et al., Sun P et al. and Hu Y et al. who reported fever, cough, fatigue and dyspnea as the most common clinical symptoms in COVID-19 patients.[16–18] Li shi et al. in their meta-analysis observed that dyspnea, rather than fever, is recommended as an indicator of poor outcome in COVID-19 patients.[19]

Laboratory abnormalities, particularly hematological changes, allow checking the status of SARS-CoV-2 infection, since the hematopoietic system and hemostasis suffer significant impacts during the evolution of COVID-19.[20] The most common hematological findings in COVID 19 infection are lymphocytopenia,[4–6] neutrophilia,[7,8] eosinopenia,[6,9,10] thrombocytopenia[6] and, less frequently, thrombocytosis.[11] The presence of reactive lymphocytes has been reported only occasionally.[21] The leukocyte count may be normal, reduced[6,22] or increased.[23] According to a *study*, leukocytosis, lymphopenia and thrombocytopenia are associated with significant disease severity and even increased fatality in COVID-19 cases.[24] In our study, most common hematological abnormality was anemia followed by neutrophilic leukocytosis, lymphocytopenia and thrombocytopenia. 3 cases had thrombocytosis. Absolute monocytosis was present in 10 cases. Absolute eosinophil count was normal in all patients. The CBC findings prompted peripheral blood smear evaluation in these patients.

On peripheral smear examination, morphologic abnormalities in the granulocytic series, namely Acquired Pelger Huet Anomaly and left shift, are significantly more common in COVID-19 cases.[25] However, leukoerythroblastosis is an uncommon finding in these patients.

Leukoerythroblastosis, is the presence of immature cells of the myeloid series and nucleated red cells in the circulating blood, with or without anemia and is not seen exclusively in malignancies. Although it is typically associated with marrow infiltrative processes, it may also represent marrow response to stressors like hypoxia, peripheral destruction/sequestration, or sepsis.[26] However, it can rarely be seen in viral infections such as parvovirus.[27,28] Isolated leukoerythroblastosis resembling leukemia may also be seen in severe infections.[29] Leukoerythroblastic reaction is always an abnormal finding.

To the best of our knowledge, there are two case reports and one study till date that describe this finding in COVID 19 infection. One in a

Table 4
Correlation of follow up (Day 7) peripheral smears of mild (n=10)/moderate (n=1) and severe (n=22) groups with clinical outcome.

Findings of follow up smears on Day 7 in mild/moderate/severe groups (n = 33)		No. of patients recovered and discharged (n = 12)	No. of patients expired (n = 19)	Clinical outcome not known (n = 2)
Improved (n = 12)	Mild/moderate	10	–	–
	Severe	–	2	–
Worsened (n = 10)	Mild/moderate	–	–	–
	Severe	1	9	–
No change (n = 3)	Mild/moderate	1	–	–
	Severe	–	2	–
Not available (n = 8)	Mild/moderate	–	–	–
	Severe	–	6	2

Table 3
Hematological parameters on admission.

CBC findings	Anemia (Hb < 12.5 g/dL)	Leukocytosis (TLC >11 × 10^3/μL)	Thrombocytopenia (Platelet Count <150 × 10^3/μL)	Thrombocytosis (Platelet Count >400 × 10^3/μL)	Neutrophilia (Absolute neutrophil count >7.5 × 10^3/μL)	Lymphopenia (Absolute Lymphocyte count <1 × 10^3/μL)	Monocytosis (Absolute Monocyte count >1 × 10^3/μL)
(n = 33)	(82%) (n = 27)	79% (n = 26)	48% (n = 16)	9% (n = 3)	76% (n = 25)	55% (n = 18)	30% (n = 10)

COVID-19 adult with respiratory failure[30] and other in a 7-year-old child with SARS-CoV-2–associated multisystem inflammatory syndrome.[31] In their studies, N Kaur et al. described this finding in 3 cases[32] while Nazarullah et al. noted leukoerythroblastosis in one case.[25] Our findings of peripheral blood smears on day 1 of admission were consistent with a leukoerythroblastic picture in 33 cases (12%). Smears showed NRBC/100 WBCs ranging from 1% to 10%, anisocytosis, and rare dacrocytes. Left shifted myeloid cells, including band forms, meta-myelocytes/myelocytes, promyelocytes and occasional blasts with or without neutrophilia was noted. Lymphopenia was confirmed in many cases. Platelets were reduced in most cases.

Except for myeloid neoplasms, left shift of granulocytes is interpreted as a sign of bacterial infection. Neutrophil activation in bacterial infections is thought to trigger mobilization of marrow reserves, resulting in granulocytic left shift.[33] In SARS-CoV-2 cases, disease induced cytokine release causing neutrophil migration similar to bacterial infection is a possible cause for leukoerythroblastosis. Direct myelotoxicity caused by the virus or increased marrow production due to increased peripheral cell turnover may be the other causes. On admission, none of our patients had any evidence suggestive of septicemia or an underlying myeloid neoplasm or malignancy causing a myelophthisic process and none had received chemotherapy or growth factors in the recent past. Two patients, however, developed sepsis later during the hospital stay. In view of absence of an underlying cause, leukoerythroblastosis in our cases thus, may represent marrow stress and response to the COVID 19 viral infection.[27–29] Most patients in our study, had comorbidities at presentation, which included hypertension, Type 2 Diabetes Mellitus, hypothyroidism, pregnancy, chronic kidney disease.

Follow up smears on day 7 were available in 25 (76%) cases (Table 4). In 12 cases, the peripheral smear findings showed improvement. Out of these, 10 cases (mild category) were discharged after recovery, while 2 patients expired (severe category). 10 cases (severe category) showed worsening of smear findings on day 7 as compared to day 1. Of these, 9 patients expired and 1 was discharged after recovery. Among the 3 cases who had no changes in follow up smears, 1 patient (moderate category) was discharged and other 2 expired (severe category). The follow up smears of 8 patients (24%) (severe category) were not available for review as 6 of these patients expired and 2 were discharged on request before the completion of day 7 after admission.

There were total 19 deaths (58%). Most of these patients showed worsening of smear findings on day 7 and all belonged to severe category. This observation strongly suggested that leukorythroblastosis confers a poor prognosis. 12 patients (36%) (10 mild, 1 moderate and 1 severe) recovered and were discharged. Following clinical improvement in these patients, leukoerythroblastosis and other blood findings on follow up blood smears improved. Clinical outcome of 2 patients (6%) was not known.

Although, all these patients had leukoerythroblastosis on admission, examination of follow up smears showed changes in most of the patients, which revealed the ongoing disease process and subsequent prognosis in them. Therefore, review of follow up smears in patients with leukoerythroblastosis irrespective of flagging for abnormalities on automated cell counter was important in correlating the findings with the clinical outcome of these patients.

We acknowledge the limitations of our study, especially the number of follow up peripheral smears that were available for review. Larger series of cases with more number of peripheral smears for review during and after treatment will be of great interest, to study the possibly transient nature of leukoerythroblastosis and its correlation with disease activity.

5. Conclusion

Leukoerythroblastosis is an unfamiliar finding in patients with COVID 19 infection. Although, it cannot be definitely concluded that this finding is secondary to COVID 19 infection, worsening of smear findings in severe and deceased patients and improvement of smear findings in mild and recovered patients is highly suggestive that SARS-CoV-2 infection is the likely cause of leukoerythroblastosis in the absence of other known causes. This Peripheral blood abnormality can thus, provide insight into the underlying pathophysiologic processes and help broaden awareness of the spectrum of COVID 19 infection. Furthermore, it seems to be an adverse prognostic factor, so examination of peripheral smears is an important work up for prognostication along with already established sets of investigation as it may help clinicians and intensivists to make prompt management decisions. However, as per our understanding of COVID 19 infection the implications of this finding are yet to be unveiled.

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Declaration of competing interest

None declared.

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