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MDS-Type Morphologic Abnormalities of Peripheral Blood Granulocytes in Symptomatic COVID-19 Patients

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ABSTRACT

Background: Hematological abnormalities in COVID-19 infection included quantitative and qualitative changes and should be further characterized. Evaluation for myelodysplastic syndromes (MDS) is usually prompted by abnormal hematologic findings and the presence of dysplastic morphologies. Viral infections are considered to be the cause of dysplastic morphologies and should be considered by morphologists. There are few reports of dysplastic abnormal morphologies in patients with COVID-19 infection. However, such correlations still have to be clarified.

Materials and Methods: In the present study, we examined the granulocyte lineage morphological abnormalities in symptomatic RT-PCR-confirmed COVID patients. Peripheral blood samples were collected from 82 patients with symptomatic COVID-19. Blood smears were prepared according to the standard Wright-Giemsa staining procedure. The morphological examination was carried out by two laboratory experts.

Results: Blood smear examination revealed common myelodysplastic syndrome (MDS) type abnormalities including but not limited to pseudo-pelger nuclear lobulation (4.8%), hypogranulation (7.3%), Howell-Jolly-like bodies or detached nuclear segments (6.0%) and elongated and thin nuclear filaments (6.0%). One case of abnormal immature granulocyte and ring form nucleus is also evident.

Conclusion: Our results accounted for the possibility of active COVID-19 infection in all subjects with granulocyte dysplasia. These results are of practical importance for patients suspected of having myelodysplastic syndromes or disease processes associated with myeloid malignancies.

Keywords: COVID-19; Myelodysplastic syndrome (MDS); Granulocytes; Morphology; Peripheral blood

INTRODUCTION

Since the onset of COVID-19 disease, several researchers have reported morphological abnormalities in peripheral blood cells[1,2,3]. Almost all blood cells showed an abnormality. As with other viral infections, attention was paid early on to atypical reactive lymphocytes as the most important morphological abnormality. However, myeloid cells also show striking changes, including dysplastic abnormalities[4,6]. An investigation for myelodysplastic syndrome (MDS) is usually prompted by abnormal hematologic findings. Blood smears show various cytopenias and dysplastic changes[7,8]. While the definitive diagnosis of MDS

requires a bone marrow examination, a peripheral blood smear is mandatory. Identifying morphological abnormalities requires an appropriate staining procedure, a fresh blood smear, and a suitably skilled and experienced pathologist. Morphologists should consider the reactive cause of dysplasia, which may include drugs, viral infections, inflammatory diseases, and nonmalignant hematologic disorders[8]. Although the impact of COVID-19 on diagnostic hematology is well documented and reviewed[9,10], new factors to consider have emerged and laboratory professionals should remain informed. In the present study, we examined the peripheral blood morphology of symptomatic COVID-19 patients.

MATERIALS AND METHODS

We examined the blood smear morphology of a cohort of symptomatic and RT-PCR-confirmed COVID-19 patients (n=82). In addition, a complete blood count (CBC) was performed on all patients as a routine laboratory test. Informed consent was obtained from all participants and the institutional ethics committee approved the present study. Blood samples were collected from September 2021 to March 2022 at Aliasghar Hospital (Shiraz University of Medical Sciences, Shiraz, Iran). Peripheral blood smears were prepared using the Wright-Giemsa staining method. Morphological examinations were carried out by two experienced morphologists. Abnormal myeloid morphologies were scored as positive if they occurred with a frequency of 5% or more. This detection limit was not applied to the presence of abnormal immature granulocytes. Patients with a history of hematologic malignancy or morphologic findings suggestive of leukemia were excluded from the study (one case). Demographic data was collected from medical records. This is a descriptive study and each abnormal morphology is reported by its relative frequency.

RESULTS

In this study, common MDS-type abnormal morphologies caught our attention; These abnormalities included cytoplasmic hypogranulation, pseudo-pelger huet anomaly, abnormal chromate clumping, Howell-Jolly-like bodies, detached nuclear segments, hypersegmented neutrophils, nuclear border irregularities, abnormal nuclear filaments, ring-shape nucleus, and abnormal immature granulocytes. Hypersegmented neutrophils and nuclear border irregularities were the most common abnormal morphologies found in the present study (9.7%). Since these anomalies were observed together in most cases, we assigned them to the same group (Figure 1-F). Cytoplasmic hypogranularity was found in 7.3% of cases. Morphologies with a two-thirds or more reduction in neutrophil granule content were considered hypogranular[11]. While some neutrophils presented an almost entirely agranular cytoplasm (Figure 1-C), hypogranulation was sometimes associated with other abnormal morphologies. Abnormal chromatin clumping, identified by large blocks of chromatin separated by clear zones, was noted in 7.3% of patients (Figure 1-D). The incidence of detached nuclear lobes and Howell-Jolly-like bodies was 6% (Figure 1-A). Abnormal and elongated nuclear fragments between segments were noted in 6% of patients (Figure 1-H). Two-lobed neutrophils and a pseudo-pelger huet anomaly were present in 4.8% of blood smears. One patient presented with granulocyte progenitors with an abnormal distribution of cytoplasmic granules (Figure 1-E). A ring-shaped nucleus was determined in one peripheral blood smear (Figure 1-D). Patient demographics and frequency of MDS-type morphologic abnormalities are summarized in Table 1. Dysplastic morphological changes are shown in Figure 1.

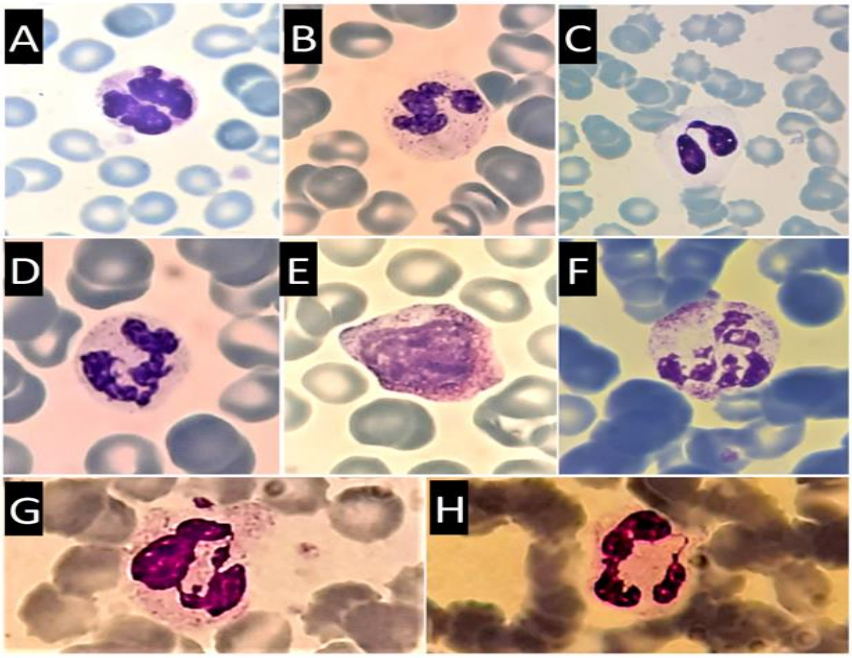

Figure 1. Granulocyte morphological abnormalities in COVID-19; A, two nuclear lobes without connecting filaments, detached nuclear bodies at the periphery of the upper lobe are recognizable. B, scarce, unevenly distributed granules. C, typical pseudo-Pelger nuclear lobe with liquefied chromatin and almost entirely agranular cytoplasm. D, Nuclear appendages of varying sizes accompanied by abnormal chromatin clumping. E. unexpected presence of eosinophilic myelocyte with uneven granule distribution. F. Hypersegmented neutrophil with irregular lobes. G. The ring forms nuclei with malformed filaments between segments. H. Elongated thin nuclear filament.

Table 1: Demographic data

Age; ranges (median)	25-93 (51.2) Y
Sex	F=31(38%)/M=51(62%)
WBC; range (median)	2200-34700 (9464) /µl
Hb; range (median)	7.1-19.9 (14.1) g/dl
PLT; range (median)	12-691 (213) $\times 10^3$/µl
Frequency of morphologic abnormalities; n(%)	
Hypogranulation	6(7.3%)
pseudo-pelger nuclear lobulation	4(4.8%)
Abnormal chromatin clamping	6(7.3%)
Abnormal immature granulocyte	1(1.2%)
Howell-Jolly-like bodies & detached nuclear segments	5(6.0%)
Hypersegmented neutrophil & nuclear border irregularity	8(9.7%)
Elongated and thin nuclear filaments	5(6.0%)
Ring form nucleus	1(1.2%)

DISCUSSION

Our study revealed dysplastic granulocytes in a group of symptomatic COVID-19 subjects. when examining a smear for morphological abnormalities, pathologists should be aware of artifacts and MDS-like reactive changes in blood and bone marrow smears[8,12]. Viral infections such as HIV are associated with marked dysplastic changes in the bone marrow[4]. In the present study, we detected both cytoplasmic and nuclear abnormalities in peripheral blood granulocytes. Detached nuclear lobes and Howell-Jolly-like bodies were noted in some patients (6%). A case report of Howell Jolly-like bodies in patients with COVID-19 has already been presented in the literature[5]. In addition to MDS, this abnormal morphology has also been reported to be found in other viral infections, including HIV1[14,15]. Hypogranular neutrophils were common (7.3%). Consistent with our findings, Zini et al. also reported hypogranular and MPO-deficient neutrophils in a group of COVID-19 patients[6]. In our cohort, pseudo-pelger huet nucleus and agranular cytoplasm were found simultaneously in some patients. This is a characteristic neutrophil anomaly of the MDS type[8,11,13]. Case reports of pseudo-pelger huet anomaly in patients with COVID-19 have been documented by Akcabelen et al.[3] and others[17,18,19]. Irregular nuclear projections were detected in our cohort. This type of change is more likely to affect MDS than reactive states[12]. We could find no reports of irregular nuclear ejection morphology in other studies. One patient presented with immature granulocytes (eosinophilic precursors) with uneven granule distribution. In the context of MDS, dysplastic immature granulocytes are more common in bone marrow smears; However, they may be detectable in blood smears from high-grade MDS[16]. Peripheral blood immature granulocytes were reported by other groups but with no evidence of dysplastic changes[17,20]. Another relatively common finding was hypersegmented neutrophils. This morphology is not specific to MDS and is usually found in megaloblastic anemia, uremia, and severe iron deficiency[8, 11]. Abnormal long and thin nuclear filaments were also identified (6%). Among them, few cells with myelokathexis-like thin interlobular strands were observed. The ring-shaped nucleus is a well-known neutrophilic dysplasia in MDS[11]. We also document this anomaly (one case). This type of abnormality was reported by Jain et.al in a group of 80 patients with COVID-19[19].

Dysplasia and morphologic abnormalities in MDS contribute to a specific form of cell death known as pyroptosis[21]. Interestingly, pyroptosis is thought to be one of the main mechanisms for cell death and leukopenia in COVID-19[22]. Both entities likely share a similar cellular mechanism for cell death and dysplasia. Further investigations are required to elucidate the exact pathophysiological mechanisms. From a diagnostic perspective, it should be kept in mind that dysplastic changes are also important for the classification and prediction of disease progression in other myeloid malignancies[23].

In addition to the peripheral blood smear, morphological abnormalities related to COVID-19 should also be considered in the bone marrow examination. Since there are no specific diagnostic biomarkers for MDS and the diagnosis is mainly based on morphological findings and cytogenetics, the diagnostician should consider distinguishing between active COVID-19. Our study suffers from the small sample size, but based on these findings and other reports, myeloid cell abnormalities are not uncommon in COVID-19 patients[10]. When such results are reproduced by other investigations, reflex COVID-19 testing and a watchful waiting strategy can avoid unnecessary bone marrow testing. Further studies are needed to confirm our results.

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