Case Report

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Concurrent dermatological manifestations, COVID-19 infection, and MDS/RCMD-RS: A unique case report

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ABSTRACT

A 24-year-old male with refractory cytopenia with multilineage dysplasia and ring sideroblasts (MDS/RCMD-RS) who developed severe dermatological manifestations concurrent with COVID-19 infection. The patient exhibited complex vasculitic and purpuric skin lesions, which were hypothesized to result from COVID-19-induced endothelitis and vasculitis, exacerbated by underlying immune dysfunction from MDS. Despite treatment with EPO therapy, cyclosporin, and supportive care, the patient's condition deteriorated rapidly, leading to fatal respiratory failure. The report underscores the interplay between hematologic malignancies, immune dysregulation, and COVID-19, highlighting the potential for exacerbated dermatological and systemic complications in such patients. This case emphasizes the need for heightened vigilance and tailored management strategies for MDS patients infected with COVID-19.

Keywords: Myelodysplastic syndrome, COVID-19, vasculitis, dermatological manifestations, immune dysfunction

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INTRODUCTION

Familial myelodysplastic syndrome (MDS) is gaining recognition as a potentially underdiagnosed clinical entity. Its occurrence within families is likely underestimated, partly due to the lack of extensive databases for documented cases and gene exploration.[1] Effectively managing patients with familial MDS and addressing risks among family members requires a deeper understanding of the genetic factors involved.[2] The connection between familial MDS and bone marrow failure syndromes, such as Fanconi anemia, dyskeratosis congenita, and Shwachman–Diamond syndrome, highlights the intricate interplay of genetic predispositions that can lead to the development of MDS.[3,4]

Systemic vasculitis is a rare, multisystem autoimmune disorder that can lead to major organ dysfunction, often necessitating intensive immunosuppressive therapy and higher doses of glucocorticoids to induce and maintain disease remission.[5] COVID-19 has been reported to trigger vasculitis through various mechanisms impacting the vascular system. Studies have revealed that the virus can directly infect the endothelial cells, leading to diffuse endothelial inflammation. This process progresses to

endothelitis, apoptosis, and pyroptosis, contributing to vascular damage. Post-mortem analyses of COVID - affected patients have shown mononuclear cell infiltrations in the vascular intima, indicating the virus's ability to invade human vasculature and cause vasculitis.[6] Additionally, COVID-19-induced vasculitis often progresses from a type 2 T-helper immune reaction to type 3 hypersensitivity. This transition is linked with the accumulation of immune complexes within the walls of blood vessels, which initiates a more intense inflammatory response. Interleukin-6 has been identified as a key mediator in this scenario, further highlighting the complex interplay between the virus and the immune system in the development of vasculitis during COVID-19 infection.[6,7]

CASE PRESENTATION

A 24-year-old male, married with no children, presented to a hematology center in April 2019 with anemia and thrombocytopenia. Initial blood work showed microcytic, hypochromic red cells (red blood cell count RBC: 3.83 x 10^6/µL, hemoglobin Hb: 8.5 g/dL,mean cell volume MCV: 74.9 fL) and a low platelet count (60,000/mm³), with a white blood cell WBC count of 6.19 x 10^3/µL. Bone marrow study revealed hypercellularity with dysplastic megakaryocytes, displaying microforms and large forms with dysplastic nuclei. Erythropoiesis exhibited hyperplasia with megaloblastoid maturation and abnormal mitotic figures, along with cells containing siderotic granules. Myelopoiesis revealed a predominance of early and intermediate forms, with a decrease in mature forms, characterized by hypogranularity, abnormal cell segmentation and granulation, and few pseudo-pelger cells. The blast count was low at 0.2%, and iron staining indicated elevated stores, with a significant 29% of abnormal ring sderoblasts. These findings collectively suggest a diagnosis of refractory cytopenia with multilineage dysplasia and ring sideroblasts (MDS/RCMD-RS).

To rule out differential diagnoses, various laboratory parameters were assessed. Hepatic function test results were obtained, including aspartate transaminase (AST) at 26 U/L, alanine transaminase (ALT) at 20 U/L, total bilirubin at 0.61 mg/dL, and direct bilirubin at 0.16 mg/dL. Alkaline phosphatase was at 61 U/L, while lactate dehydrogenase was elevated at 518 U/L. Urea, creatinine, sodium, and potassium were recorded at 25 mg/dL, 0.8 mg/dL, 143 nmol/L, and 4.6 nmol/L, respectively. No evidence of solid neoplasms, thyroid dysfunction, autoimmune diseases, or infections was reported. The patient tested negative for hepatitis B, hepatitis C, and Human immunodeficiency virus(HIV) Vitamin D levels were measured at 18.2 ng/ml, and vitamin B12 levels were at 585 pmol/L. Furthermore, karyotype analysis conducted on the bone marrow sample using Giemsa-trypsin-Giemsa (GTG) banding revealed a normal male clone with a karyotype of 46XY in all the analyzed metaphases.

The patient was treated with EPO therapy thrice per week and cyclosporin at 200 mg twice per day, maintaining a blood level around 333.5 ng/ml for six months. Efforts made for HLA matching with his sister revealed a full match. Unfortunately, the sister succumbed to the same condition. The patient initially responded positively, with improvements in peripheral blood parameters after two months (RBC count: 3.4106/µL, Hb: 8.2 g/dL, MCV: 76 f/L, platelet count: 134,000/mm³, and WBC count: 30103/µL). However, the improvement was temporary, and the condition worsened leading to transfusion dependence despite ongoing treatment. In July 2020, the patient presented with fever, shortness of breath, cough, ecchymosis, hemorrhagic bullae, and other skin lesions. His peripheral blood film showed an RBC count of 2.3106/µL, Hb of 6.9 g/dL, MCV of 75.9 f/L, platelet count of 15,000/mm³, and WBC count of 23.1103/µL, with 2% primitive cells. Biochemical tests revealed elevated total bilirubin (3.2 mg/dL), direct bilirubin (3 mg/dL), AST (30 U/L), ALT (39 U/L), and ALK (353 U/L). LDH was notably high (1964.94 U/L). Renal function was impaired (serum creatinine 2 mg/dL, blood urea 180 mg/dL), D Dimer was elevated (9635 ng/l), and serum ferritin exceeded 2000 ng/ml.

The patient tested positive for COVID-19 and was isolated at a teaching hospital. During this period, he experienced a high-grade fever and oxygen desaturation. He received convalescent plasma, dexamethasone, antibiotics, and vitamins. Transfusions of PRBC and platelet concentrate were administered twice. Although the skin lesions resolved, his respiratory condition deteriorated suddenly, raising concerns of pulmonary embolism. The patient passed away within a few days.

The dermatological presentation involved complex vasculitic or purpuric lesions on upper and lower limbs, with some on the chest. Lesions varied in size, with larger

ones on the lower legs and feet and smaller ones on the forearms and upper legs. The upper limbs had bullous lesions with clear fluid, some showing purpuric centers and peripheral exfoliation. (Fig.1)

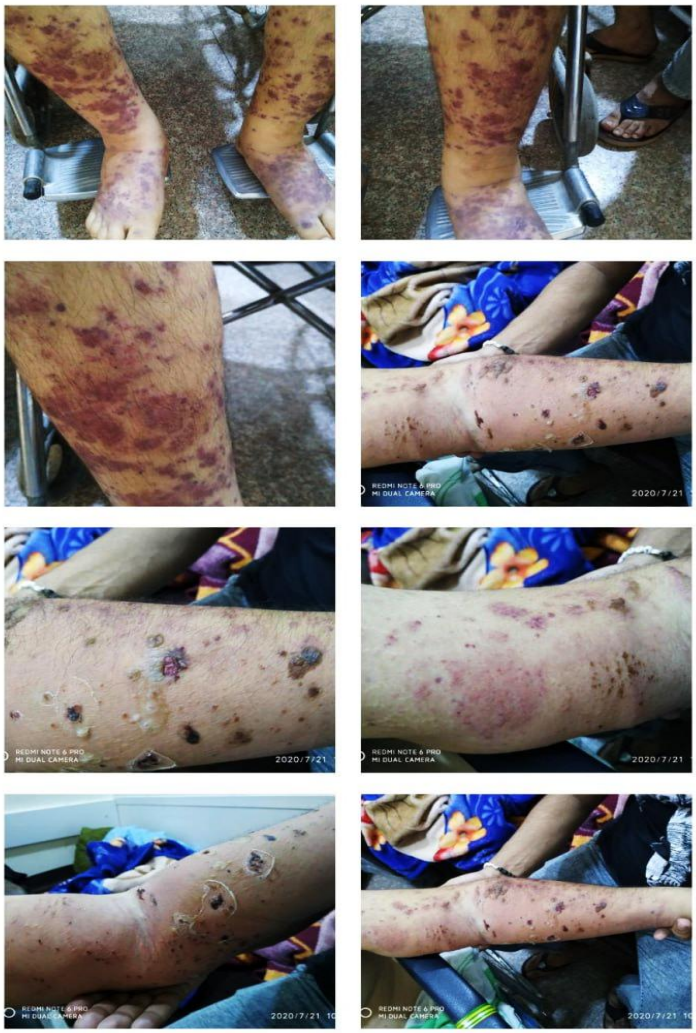

Figure 1: The patient's initial presentation in the emergency department, featuring ecchymosis, vasculitic or purpuric lesions, and hemorrhagic bullae, some with clear fluid and others showing purpuric centers and peripheral exfoliation.

DISCUSSION

Hematologic malignancies pose unique challenges among COVID-19 patients due to their impact on the immune system.[8,9] The associated immune dysfunction increases the vulnerability to COVID-19 and worsens the disease progression in affected patients. In particular, weakened T-cell responses may contribute to the unfavorable outcome of COVID-19 in individuals with hematologic malignancies. In their study, Bilich et al. showed that both the pre-existing and newly formed CD4 T-cell reactions to SARS-CoV-2 in patients with hematological malignancies are impaired.[10] Similarly, Langerbeins et al. reported that patients with hematologic malignancies exhibited significantly diminished intensity, expandability, and diversity of preexisting SARS-CoV-2 cross-reactive CD4+ T-cell responses. They also displayed signs of T-cell exhaustion compared to patients with solid cancer or healthy controls.[11]

Potent immunosuppressive therapies, including hematopoietic stem cell transplantation, contribute to further impairment of immune function.[12,13] Kim et al., in a systematic review on clinical characteristics and mortality, found that patients with these malignancies had significantly higher COVID-19 mortality rate compared to those without malignancies (40.0% vs. 3.6%).[14] In their multicenter study in China, Yang et al. investigated 205 cancer patients and found an overall mortality rate of 20%. Of these, 22 patients had

hematologic malignancies, experiencing a significantly higher mortality rate of 41%.[15]

Several risk factors contribute to adverse outcomes in COVID-19 patients with hematologic malignancies, including advanced age, comorbidities, active hematologic malignancy, specific types of hematologic malignancies, ICU admission, mechanical ventilation requirement, and severe COVID-19 illness.[11] A report from the ASH Research Collaborative Data Hub by Woods et al. advocates against withholding intensive life-sustaining interventions from these patients, especially those with a favorable prognosis. Additionally, individuals with hematologic malignancies should be vaccinated.[16]

The multifactorial etiology behind the observed dermatological manifestations in the studied patient may primarily be attributed to COVID-19-associated endothelitis and vasculitis. Varga et al. provided evidence of direct viral invasion causing endothelial damage, leading to widespread vascular inflammation and damage in the blood vessel lining, as seen in post-mortem examinations. They also noted the infiltration of certain immune cells into the vessel walls, indicating the virus's ability to cause vasculitis.[6] Roncati et al. expanded on this mechanism, explaining how the immune response shifts from one type to another in COVID-19-induced vasculitis. They found that immune complexes build up in the vessel walls, worsening inflammation, with interleukin-6 playing a crucial role in this process.[17] Other external signals and intracellular mediators, including anti-inflammatory cytokines, are also involved.[18] Additionally, ACE2 receptors within endothelial cells could play a role in viral binding, membrane fusion, and entry, potentially resulting in infection, vascular injury, and dysfunction.[19] Another mechanism is activation of the coagulation cascade and complement-mediated microvascular injury. In severe cases, this can result in various coagulation disorder-associated skin manifestations, indicating a critical systemic hypercoagulable state.[20]

Regarding prognosis, the presence of transient livedo reticularis may reflect low-grade thrombosis, suggesting a less severe condition.[21] Chilblain-like lesions, induced by released cytokines or microthrombi, may aid in diagnosing asymptomatic patients and could also signal a favorable prognosis. Conversely, severe disease is characterized by extensive thrombosis, leading to manifestations such as livedo racemosa, retiform purpura, acrocyanosis, or limb ischemia.[20,22] Besides, a study by Suchonwanit et al. suggests that while certain skin lesions resembling viral exanthems may not offer specific clues for diagnosing or predicting COVID-19 outcomes, manifestations linked to vasculopathy, such as chilblain-like lesions and vasculitis, may provide valuable prognostic indicators. Early identification of severe skin signs associated with severe disease is vital for better outcomes.[23]

While this study highlights the skin manifestations observed in an MDS patient with COVID-19, direct comparisons with MDS patients who are not infected with COVID-19 remain limited in the literature. The lack of comparative studies makes it challenging to definitively attribute specific skin manifestations solely to COVID-19 in MDS patients. However, general observations suggest that COVID-19-related skin symptoms, such as vasculitis, livedoid eruptions, and purpuric lesions, may be more prominent in patients with hematologic malignancies, including MDS, as these individuals have a high vulnerability due to compromised immune systems. Given COVID-19's impact on the vascular and immune systems, it is plausible that MDS patients with COVID-19 may experience exacerbated or distinct dermatologic symptoms compared to MDS patients without COVID-19.[9,10] These manifestations could stem from COVID-19-associated endothelial dysfunction and immune-mediated inflammation,[17–19] which are less commonly observed in non-COVID MDS cases. This suggests that COVID-19 might intensify underlying vulnerabilities in MDS patients, particularly those related to immune dysregulation and vascular integrity.

CONCLUSIONS

In summary, this case study highlights significant dermatological manifestations in an MDS patient with COVID-19, suggesting that the viral infection may exacerbate or trigger more severe skin conditions, likely due to the interplay of immune dysfunction and vascular inflammation. Although data comparing MDS patients with and without COVID-19 remain limited, the findings suggest that COVID-19 may worsen skin complications in MDS. Future studies are essential to confirm these observations and guide patient care.

Declaration of Patient Consent: The authors have obtained patient consent for the publication of images and clinical details in this journal. The patient has been informed that anonymity will be maintained to the best of the journal's efforts, although complete anonymity cannot be guaranteed.

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