SHORT COMMUNICATION

COVID-19 related immune hemolysis and thrombocytopenia

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Abstract
The current pandemic due to coronavirus disease 2019 (COVID-19) has posed an unprecedented challenge for the medical communities, various countries worldwide, and their citizens. Severe acute respiratory syndrome coronavirus 2 has been studied for its various pathophysiological pathways and mechanisms through which it causes COVID-19. In this study, we discussed the immunological impact of COVID-19 on the hematological system, platelets, and red blood cells.

KEYWORDS
coronavirus, hemolysis, immunity

1 | INTRODUCTION

Currently, the world is trampled by the coronavirus disease 2019 (COVID-19) with more than 18 million cases and 695,129 deaths already reported (till 8th August 2020). Due to the novelty of COVID-19 disease, there is an ongoing effort by basic science researchers and clinicians worldwide to learn more about this disease. Complement activation, immune dysregulation, and coagulation cascade perturbations have been studied as the most potential pathophysiological mechanisms for COVID-19 disease. Recent reports of immune effects of COVID-19, such as immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA), suggest the pathological interaction between coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) and various immune and tissue cells of our body. We hereby aim to summarize the collected reports of ITP and AIHA secondary to COVID-19 reported to date.

2 | METHODOLOGY AND RESULTS

In our literature search, we found 20 patients with COVID-19 who were reported to have immune dysregulation with the development of ITP, AIHA, and/or Evan’s syndrome. In total, there were 10 (50%) patients with ITP, 9 (45%) patients with AIHA, and 1 (5%) patient had Evan’s syndrome. The average age of the patients was 61 (17-89 years) with the majority (55%) being males (11 out of 20). Four out of 20 (20%) patients also had a previous history of autoimmunode disease (one each with polymyalgia rheumatica and autoimmune hypothyroidism, and two with chronic ITP). To note, one (5%) patient also had congenital thrombocytopenia. Regarding the underlying malignancies, eight (40%) patients were found to have history of cancers, six with lymphoproliferative disorders (CLL-2, MZL-2, MGUS-1, and ALPS-1) and the remaining two with solid malignancies. The largest case series of AIHA with COVID-19 (7 cases) to date has been reported by Lazarian et al.

Our review showed that most patients who had bleeding symptoms only reported of superficial bruising, petechial spots, or hemorrhages. Only 2 patients out of 20 (10%) suffered from intracranial bleeding, one out of which died. Reported nadir platelet counts in ITP cases were extremely variable with as high as 338,000 cells/µL to as low as 0 cells/µL. Similarly, the lowest reported hemoglobin (2.5 gm/dL) in AIHA with COVID-19 was reported by Wahlster et al. All patients were laboratory-confirmed COVID-19 positive with a positive nasopharyngeal swab. With regard to the management, drugs attempted were steroids (dexamethasone, methylprednisone, and prednisone), intravenous immunoglobulin (IVIG), eltrombopag, and rituximab (Table 1). Most of the patients (four out of seven) with AIHA reported by Lazarian et al were receiving treatment at the time of publication. Two patients had a partial response and one patient failed to respond to steroids. All nine patients (100%) with AIHA and 9 of 10 patients (90%) with ITP recovered from the acute crisis and were discharged.
| Author et al | Age | Sex | Previous comorbidities | Underlying malignancy | Diagnosis | Symptoms | Bleeding signs/sites | Zenith WBC, cells/µL | Lymphocyte count, 10^9/L | Nadir Hb, g/dL | Nadir platelet count, cells/µL | Reticulocyte count, 10^9/L | LDH | Other laboratory workup | Chest imaging | ITP/Evans’s treatment |
|--------------|-----|-----|------------------------|-----------------------|-----------|----------|---------------------|------------------------|-----------------------|--------------|---------------------------|--------------------------|-----|------------------------|--------------|---------------------|
| Li et al     | 39  | Male| None                   | None                  | Evans’s syndrome (new onset) | Hemoptysis and epistaxis ×1 d, sore throat, productive cough, fevers, chills, and dyspnea ×7 d | Oropharynx, nares, and mouth | 11 000 | 15.6 | 3000 | NA | 947 | Hemolytic panel negative, no schistocytes | Normal | IVIG |
| Lazarian et al | 61  | Male| HTN, CRF               | Chronic lymphocytic leukemia | AIHA (warm type) | NM | NM | NM | 250 | 6 | NM | 477 | 1000 | Coombs test positive (IgG + C3d) | Moderate | Steroids |
| Lazarian et al | 89  | Female| HTN, CRF, AFIB | MGUS | AIHA (warm type) | NM | NM | NM | 1.7 | 8.4 | NM | 103 | 598 | Coombs test positive (IgG + C3d) | Mild | Steroids |
| Lazarian et al | 62  | Female| HTN, cirrhosis        | MZL | AIHA (cold type) | NM | NM | NM | 1.3 | 10.8 | NM | 101 | 357 | Coombs test positive (C3d) | Severe | Steroids, rituximab |
| Lazarian et al | 69  | Female| Obesity, HTN          | MZL | AIHA (cold type) | NM | NM | NM | 5.9 | 3.8 | NM | 215 | 2610 | Coombs test positive (IgG + C3d) | Moderate | Steroids |
| Lazarian et al | 61  | Male| CRF, HLD, type 2 DM   | Prostate cancer | AIHA (cold type) | NM | NM | NM | 3 | 7.2 | NM | 145 | 807 | Coombs test positive (C3d) | Mild | RBC infusion |
| Lazarian et al | 61  | Male| Type 2 DM, HLD        | None | AIHA (warm type) | NM | NM | NM | 1.2 | 7 | NM | 155 | 1800 | Coombs test positive (IgG) | Severe | Steroids, rituximab |
| Lazarian et al | 75  | Male| Cardiomyopathy, obesity, COPD | CLL | AIHA (warm type) | NM | NM | NM | 108 | 7.1 | NM | 98 | 2000 | Coombs test positive (IgG) | Moderate | RBC infusion |
| Bomhof et al  | 59  | Male| NA                     | Stage IV NET of the small bowel | New onset ITP | Coughing and fever 10 d, contact with a positive case | Oral mucosal petechiae and spontaneous skin hematoma | 3900 | 400 | 8.3 | 3000 | NM | Not mentioned | Platelet autoantibodies positive for GP Ib, GPIBiIIa, and GPV | SVAD, IVIG, dexamethasone |
| Bomhof et al  | 66  | Female| HTN                    | New onset ITP | Fever, dyspnea, and coughing | Petechiae, ecchymosis | 5800 | 700 | 8 | 2000 | NM | NM | Platelet | NM | (Continues) |
| Author et al | Age | Sex | Previous comorbidities | Underlying malignancy | Diagnosis | Symptoms | Bleeding signs/sites | Zenith WBC, cells/µL | Lymphocyte count, 10³/L | Nadir Hb, g/dL | Nadir platelet count, cells/µL | Reticulocyte count, 10⁹/L | LDH | Other laboratory workup | Chest imaging | ITP/Evans’s treatment |
|-------------|-----|-----|------------------------|-----------------------|-----------|----------|---------------------|---------------------|---------------------|--------------|-----------------------------|----------------|------|--------------------------|--------------|--------------------------|
| Bomhof et al | 67  | Male| HTN, type 2 DM         | ITP                   | Fever, coughing, and dyspnea ×9 d | 11 200   | 860     | 9.3                | 338 000         | NM                | NM           | Platelet autoantibodies testing and viral serology testing not done | Bilateral infiltrates | Dexamethasone, IVG |
| Lopez et al  | 46  | Female | Congenital thrombocytopenia | None | AIHA (warm) | Dyspnea and cough | 9850    | 680    | 9.7            | 43 000        | 206           | 553          | Coombs test positive (IgG + C3d), ANA was negative | Dense left upper lobe consolidation with minimal surrounding ground-glass opacities and no evidence of pulmonary embolism | IVG |
| Tang et al  | NA  | Female | None | New onset ITP | Sore throat | No bleeding | NM | NM | NM | 16 000 | NM | NM | | | |
| Author et al | Age | Sex | Previous comorbidities | Underlying malignancy | Diagnosis | Symptoms | Bleeding signs/sites | Zenith WBC, cells/µL | Lymphocyte count, 10^9/L | Nadir Hb, g/dL | Nadir platelet count, cells/µL | Reticulocyte count, 10^9/L | Other laboratory workup | Chest imaging | ITP/Evans’s treatment |
|--------------|-----|-----|------------------------|-----------------------|-----------|----------|---------------------|---------------------|----------------------|----------------|-----------------------------|--------------------------|--------------------------|---------------|----------------------|
| Zulfiqar et al | 65  | Female | HTN, autoimmune hypothyroidism | None | New onset ITP | Fatigue, fever, dry cough, and abdominal discomfort of 4 d | Lower-extremity purpura, subarachnoid microhemorrhage | Normal | NM | 14.2 | 1000 | NM | NM | Antiplatelet antibodies and antinuclear antibodies were not detected | Ground-glass opacities in the lower zones | IVIG, platelet transfusion |
| Hu et al | 72  | Female | Chronic ITP (in remission with prednisone [10 mg/d] and cyclosporine [50 mg/d]) | None | Relapse of chronic ITP | Productive cough × 4 d and fever × 1 d | None | None | 2550 | NM | 18000 | NM | LDH | None | Peripheral ground-glass opacity in the right lower lobe | IVIG, platelet transfusion, methylprednisolone |
| Murt et al | 41  | Male | None | None | New onset ITP | Cough and runny nose 15 d ago | Petechiae and nasal bleeding | None | 9200 | 330 | 12.2 | 4000 | NM | NM | ANA negative, platelet antibodies negative, lupus | Diffuse ground-glass opacities and Prednisone, IVIG |
| Humbert et al | 84  | Male | Polymyalgia rheumatica, essential tremor | None | New onset ITP | Cough and progressive dyspnea × 10 d | Spontaneous macroscopic hematuria | 9200 | 330 | 12.2 | 4000 | NM | NM | ANA negative, platelet antibodies negative, lupus | Diffuse ground-glass opacities and Prednisone, IVIG |

(Continues)
| Author et al. | Age | Sex | Previous comorbidities | Underlying malignancy | Diagnosis | Symptoms | Bleeding signs/sites | Zenith WBC, cells/µL | Lymphocyte count, 10^9/L | Nadir platelet count, cells/µL | Reticulocyte count, 10^9/L | LDH | Other laboratory workup | Chest imaging | ITP/Evans’s treatment |
|---------------|-----|-----|------------------------|-----------------------|-----------|----------|---------------------|----------------------|------------------------|--------------------------|-------------------------|-----|------------------------|-------------|---------------------|
| Wahlin et al. | 17  | Male| Chronic ITP (in remission with eltrombopag and mycophenolate) | ALPS | AIHA | Worsening jaundice and fatigue in the setting of 4 d of emesis, diarrhea, and fevers | None | 4370 | 440 | 2.5 | 94,000 | NM | 1280 | IgG 3+, C3 1+ | Mild prominence of perihilar markings | Steroids |
| Ahmed et al.  | 50  | Male| None | None | New onset ITP | Asymptomatic close contact with COVID-19 positive | Epistaxis, oral blisters, and a generalized petechial rash | 4000 | NM | 13.2 | Not detected | NM | NM | Normal | IVIG, tranexamic acid |
| Ahmed et al.  | 49  | Female| None | None | New onset ITP | Asymptomatic close contact with COVID-19 positive | Generalized bruises and gum bleed | 5300 | None | 13.4 | 4000 | NM | NM | Negative | Revealed bilateral patchy consolidation | IVIG |

Abbreviations: AFIB, atrial fibrillation; AIHA, autoimmune hemolytic anemia; ALPS, autoimmune lymphoproliferative syndrome; ANA, antinuclear antibody; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRF, cardiopulmonary fitness; EBV, Epstein-Barr virus; Hb, hemoglobin; HIV, human immunodeficiency; HLD, hyperlipidemia; HTN, hypertension; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of undetermined significance; MZL, marginal zone lymphoma; NA, not applicable; NET, neuroendocrine tumor; NM, not mentioned; Parvo B19, parvovirus B19; RBC, red blood cell; type 2 DM, type 2 diabetes mellitus; WBC, white blood cell.
DISCUSSION

Thrombocytopenia is one of the challenging disease entities faced by clinicians in day-to-day clinical practice. Immune-mediated hematologic conditions, characterized by ITP, AIHA, or Evan’s syndrome, are known to be associated with previous exposure to various viral infections. Platelet-virus interplay could represent a combination of multiple pathways that may include complement activation, antigen mimicry of platelet surface glycoproteins, consumptive coagulopathy, and direct bone marrow suppression. Similarly, AIHA is a common association with indolent lymphoproliferative disorders, and the coinfection of SARS-CoV-2 could potentially trigger hemolysis (Figure 1). Treatment of autoimmune disorders is always challenging in the presence of active infection. Hematologists and other physicians often prefer IVIG as an initial therapy when the concerns of worsening of active infection or risk of acquiring a superadded infection are high. Due to concerns that steroids may worsen the SARS-CoV-2 infection and could lead to acute respiratory distress syndrome, World Health Organization (WHO) recommends against using steroids in COVID-19. In the present patient cohort, most of the patients received steroids for their autoimmune disease and not COVID-19.

CONCLUSION

In conclusion, hematological findings such as thrombocytopenia and anemia in COVID-19 could be due to multiple reasons and timely diagnosis of the immunological cause is essential, so that appropriate immunosuppression can be initiated in a timely fashion.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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