Hematologic autoimmune disorders in the course of COVID-19: a systematic review of reported cases

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ABSTRACT

Objective: As COVID-19 is a new emerging disease, the hematological/immunological changes that develop in the infected patients remain unknown. This study aims to systematically review the hematologic autoimmune complications in these patients.

Method: Data from three online databases including Medline (via PubMed), Scopus and Web of Science were searched on 19 December 2020, and after excluding duplicate, irrelevant and inappropriate records, eligible documents were identified. Afterwards, information such as patients’ history, presentations, paraclinical data, treatment course and outcome were extracted from the records.

Results: A total of 58 documents were considered to be eligible for data extraction which described 94 patients with COVID-19 who developed hematologic autoimmune disorder in their course of infection. Of these patients with COVID-19, the most common hematologic autoimmune disorder was immune thrombocytopenic purpura (55 cases) followed by autoimmune hemolytic anemia (22 cases). Other hematologic autoimmune disorders include antiphospholipid syndrome, thrombotic thrombocytopenic purpura, Evans syndrome and autoimmune neutropenia.

Conclusion: The current study would help us to always consider an autoimmune etiology for cases with abnormal hematologic finding which further lead to an appropriate treatment of the patients, especially when the symptoms present in about 1–2 weeks after the first manifestation of the infection symptoms. Maybe, at least in this pandemic, it should be recommended to evaluate patients with unexplained decrease in their hemoglobin or platelet count for COVID-19. Another challenging issue is the treatment options. Given the multiorgan involvement and multifaceted nature of the infection, an individualized approach should be taken for each patient.

KEYWORDS

Hematologic autoimmune disorders; COVID-19; SARS-CoV-2; Thrombosis; Autoimmunity; Hemolytic anemia; Thrombocytopenia; Steroids

Introduction

Late in 2019, a novel viral strain from Coronaviridae family was isolated in the throat culture of a series of patients complained of influenza-like manifestations. This newly emerged strain was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Due to its high primary attack rate, extensive containment measures including universal lockdowns and social distancing were imposed to impede the spread [2]. However, despite these preventive measures, the virus is rapidly spreading through the world turning it from a public health emergency of international concern into a pandemic, declared by World Health Organization (WHO) on 11 March 2020 [3].

While SARS-CoV-2 mainly targets the respiratory tract, with respiratory failure and acute respiratory distress syndrome as the leading cause of mortality among the afflicted patients, extra-respiratory systems’ manifestations are also frequently observed [4]. The typical clinical manifestations of coronavirus disease 2019 (COVID-19) include fever, dry cough, fatigue, sore throat, malaise and myalgia. Furthermore, there are other less common symptoms such as headache, dizziness, diarrhea and nausea and vomiting [4,5].

Recently, an increasing number of studies have demonstrated that SARS-CoV-2 infection could result in alteration in immune system functions [6]. These alterations could range from an inappropriate immune response and abnormal cytokine/chemokine production to immune system hyperactivation and dramatic increase in immune-inflammatory parameters. These vigorous immune responses could lead to autoimmunity and cytokine storm [7]. Besides, researches have reported several cases of patients with COVID-19, among whom autoimmune events were developed such as vasculitis, Guillain–Barré syndrome, etc. [8]. These findings indicate that SARS-cov-2 infection may be associated with the induction of autoimmune disorders. Among these...
autoimmune manifestations, several hematologic autoimmune disorders have been also reported and showed that could complicate the management and be in association with outcome in patients with COVID-19 [9–12]; however, they are less paid attention to. As COVID-19 is a new emerging disease, little is known about these immunological changes that occur in the afflicted patient. Given this, we aimed to systematically review hematologic autoimmune disorders reported in patients with SARS-CoV-2 to shed light on this era for better management of patients.

Method

Search sources and strategies

In the current study, a systematic review for relevant records about hematologic autoimmune events developing in the course of SARS-CoV-2 infection was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Data were gathered from three different online databases including Medline (via PubMed), Scopus and Web of Science. The search has been conducted by the third author in 16 August 2020 and updated in 19 December. In order not to miss any data, a broad search strategy was developed with a combination of key terms of both coronavirus and hematologic autoimmune disorders. The keywords used for coronavirus were COVID-19, coronavirus, SARS-CoV-2 and 2019-nCoV. Furthermore, the following keywords were considered for hematologic autoimmune disorders: autoimmune, autoimmune anemia, autoimmune hemolytic anemia, hemolytic anemia, cold agglutinin, AIHA, pernicious anemia, immune thrombocytopenia, immune thrombocytopenic purpura, idiopathic thrombocytopenic purpura, ITP, thrombotic thrombocytopenic purpura, TTP, Evans syndrome, autoimmune cytopenia, autoimmune neutropenia, antiphospholipid syndrome, anticardiolipin, Beta-2-glycoprotein, lupus anticoagulant and APS.

Study selection

Six hundred and fifty-three articles in PubMed, 1050 articles in Scopus articles and 494 articles in Web of Sciences were found following the search and then their citations were exported into endnote X9 (Clarivate Analytics, USA). At first, duplicate records (678 documents) were removed from the library and afterwards, first screening was conducted by the first and second authors; in this step, titles and abstracts of the records were evaluated in order to remove those which are clearly irrelevant; however, those records which were unclear whether they are eligible for final qualitative analysis or not were kept in the study for subsequent screening (Figure 1); in the second round of the screening process, full texts of the records were evaluated for relevancy. Records from papers with any design or methodology which did not describe the cases who developed hematologic autoimmune disorders including their presentations, their paraclinical workups, their treatment course, etc. were excluded in the second screening round. In this study, not only case reports and case series but also letters or commentaries that included information of SARS-CoV-2-infected patients with hematologic autoimmune disorders were considered eligible. Besides, not only documents of the patients with new onset of hematologic autoimmune disorders, but also documents that reported a relapse or flare of a chronic hematologic autoimmune disorder were included in the qualitative synthesis. There were no restrictions based on the country of origin or the language used in the articles. Besides, both published papers and those that are ahead of print were considered for data extraction.

Data extraction

An Excel spreadsheet was created to extract the following data: study title, first author, access date, type of study, history of the patient, the clinical symptoms and signs the patient presented with, patient’s paraclinical information, the hematologic complication observed in the patient, the treatment course including for both hematologic disorder and SARS-CoV-2 infection and the patient’s outcome. Among patients’ paraclinical workups, only those helpful for diagnosis of the hematologic disorder the patients afflicted to were gathered from the selected records.

Results

A total of 94 patients with SARS-CoV-2 infection who developed hematologic autoimmune disorders in their course of infection were included in the final analysis. Male and female patients constituted an almost equal proportion of the study cases, 47 and 44 cases, respectively. The gender status of three cases of a study was not identified in the document [14]. The study cases had a wide age range from 2 years to 94 years with a median age of 60 and the mean age of 56 ± 18.5. The elder population constitute the majority of cases with 48.9% (46 cases). There were only three pediatric cases and these three patients were all afflicted to idiopathic thrombocytopenic purpura (ITP). A majority of cases had comorbidities (69 percent); however, 14 out of 29 remaining cases were described in a study in which the underlying disorders of the patients were not reported [15]. The most common presentation in these cases was fever reported in 69 (73%) of them, followed by coughing in 56 (59%) and dyspnea in 40 patients (42%).
Among 94 patients, the most common hematologic autoimmune disorder was ITP in 55 cases (58%) followed by autoimmune hemolytic anemia (AIHA) in 22 cases (23%). Other hematologic autoimmune disorders observed in the literature include antiphospholipid syndrome (APLS) in 10 individuals, thrombotic thrombocytopenic purpura (TTP) in 3 individuals, Evans syndrome in 3 individuals and autoimmune neutropenia in one individual (Table 1). The laboratory workups which led to these diagnoses for each case is documented in Supplementary material 1.

Overall, the time of onset of the hematologic autoimmune presentations from the SARS-CoV-2 infection presentations and not from the time of COVID-19 diagnosis is demonstrated in Table 1. The mean time for all categories of hematologic autoimmune disorders was $11.8 \pm 7.1$ days (95% confidence interval of $10.4-13.3$); the mean time in ITP, AIHA, APLS, TTP and Evans syndrome were $13.3 \pm 7.3$, $8.9 \pm 5.02$, $14 \pm 7.5$, $4.6 \pm 1.5$ and $5.5 \pm 2.1$, respectively.

Among these patients, 88 patients were alive and in the recovery process and their hematological indices related to the autoimmune disorders improved. Among the deceased cases, three were with AIHA, two were with ITP and one was afflicted to APLS. All three patients with AIHA deceased early, two due to the hemodynamic collapse as a result of the hemolysis process and one due to delayed detection of intracerebral hemorrhage. Among the two deceased patients with ITP, one died of an intracerebral hemorrhage within first 24 h and the other responded significantly to the treatment but passed away due to his poor condition and not due to the autoimmune sequel. For the deceased patient with APLS, the medical team decided...
| Autoimmune hematologic complications of SARS-CoV-2 infections. | Timing of the hematologic presentations | Clinical presentations | Autoimmune disorder | Treatment | Outcome |
|---|---|---|---|---|---|
| First author | History of the patient | Clinical presentations | | | |
| Zagorski et al. | A 46 Y/O female K/C of iron deficiency anemia, asthma, splenomegaly and TIP 7 years ago | Fever, dyspnea, muscle aches, lethargy, vomiting, diarrhea, and anosmia | Autoimmune syndrome | HCQ, darunavir/ritonavir, azithromycin, favipiravir | Recovered (Hb raised on days 3 of admission after change of IVIG to steroid and patient discharged on day 15) |
| Patil et al. | 51 Y/O female K/C of breast ductal carcinoma in situ | Fever, dyspnoea, malaise, pain of ribs | Autoimmune disorder | HCQ, solumedrol, heparin, folic acid, packed cell transfusion, warm IV fluids | Recovered (Hb became stable at day 2 and patient discharged after more than 4 days) |
| Capes et al. | 62 Y/O smoker male K/C of HTN and oropharyngeal squamous cell carcinoma on chemoradiation | A weeklong history of weakness, anosmia, and decreased appetite, O2 sat: 88% | Autoimmune syndrome | HCQ, Ceftriaxone, heparin infusion, packed cell transfusion | 1. Complicated course (not much detail mentioned) 2. Recovered 3. Recovered 4. Steroid 5. Packed cell 6. Steroid, rituximab 7. Packed cell |
| Moonla et al. | – 24 Y/O female | Fever, mild dyspnea with low O2 sat, marked asthenia | Autoimmune disorder | HCQ, darunavir/ritonavir, azithromycin, favipiravir | Recovered (Hb raised on days 3 of admission after change of IVIG to steroid and patient discharged on day 15) |
| Maslov et al. | 48 Y/O male K/C of essential HTN, T1DM, obesity and end-stage renal disease on peritoneal dialysis | After 3 h of admission, his neurological status declined and he was intubated for airway protection and became hypotensive | Autoimmune syndrome | 1. HCQ, Ceftriaxone, heparin infusion, packed cell transfusion 2. Not mentioned | 1. Recovered (Hb started to raise after 1 day) 2. Steroid 3. Steroid, rituximab 4. Steroid, rituximab 5. Steroid, rituximab 6. Steroid, rituximab 7. Packed cell |
| Jensen et al. | – 70 Y/O male | Fever, cough, hypoxia | Autoimmune disorder | Ceftriaxone, tazocilline, azithromycin, packed cell transfusion 2. Not mentioned | 1. Recovered (Hb started to raise after 1 day) 2. Steroid 3. Steroid, rituximab 4. Steroid 5. Packed cell 6. Steroid, rituximab 7. Packed cell |
| Hindilerden et al. | – 56 Y/O male K/C of HTN | Dyspnea, cough, headache, loss of smell, tachycardia, tachypnea, scleral icterus | Autoimmune disorder | Tocilizumab on day 6, steroid, rituximab 1. Steroid, packed cell transfusion 2. Not mentioned | 1. Recovered 2. Deceased 3. Recovered 4. Steroid, packed cell transfusion 5. Steroid, packed cell transfusion |
| Lopez et al. | – 46 Y/O female K/C of congenital thrombocytopenia not on therapy | Fever, dyspnea, cough, diarrhea, tachycardia, O2 sat: 99% | Autoimmune disorder | Azithromycin, ceftriaxone, packed cell transfusion | About 3 days |
| Jacobs et al. | – 33 Y/O female K/C of hypothyroidism | Headache for 2 days and family concern regarding mental status. O2 sat: 99% | Autoimmune disorder | Tocilizumab on day 6, steroid, rituximab | About 5 days |
| Author(s)             | Diagnosis                          | Symptoms                                                                 | Duration | Treatment                                                                 | Outcome                                                                 |
|----------------------|-------------------------------------|--------------------------------------------------------------------------|----------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Hernández et al. [25]| Patient K/C of psoriasis           | delayed responses upon questioning and sluggish reactions to verbal commands, 7-day period of fever, asthenia, headache and a syncope episode without loss of consciousness, tachycardia with hemodynamic stability and muco-cutaneous pallor | 7 days   | AIHA Steroid                                                              | rituximab therapy, Hb began to stabilize and patient was discharged on day 13 (Continued) |
| Jawed et al. [26]    | In early 50s Y/O male K/C of uncontrolled HTN and obstructive sleep apnea | Coryzal symptoms 2 weeks prior, shortness of breath on mild exertion, diarrhea, mild jaundice yellowish discoloration of eyes, dark urine, an episode of frank per rectum bleeding, high blood pressure, O₂ sat: 96% | About 14 days | AIHA Adenosine (for supraventricular tachycardia), bisoprolol             | Recovered (patient discharged on day 33)                                  |
| D’Aloisio et al. [27]| 46 Y/O male K/C of HTN and hereditary spherocytosis | Respiratory failure and unilateral visual loss after a 12-day history of fever, worsening dyspnea and cough | 12 days | AIHA-Cold agglutinin syndrome Chloroquine, packed cell transfusion         | Recovered (patient discharged on day 13)                                  |
| Sereno et al. [28]   | 58 Y/O smoker male K/C of advanced small cell lung cancer | Fever, cough, chest pain, progressive asthenia, tachypnea 2 days | 2 days   | Possible autoimmune neutropenia due to coronavirus HCQ, meropenem, dexamethasone, granulocyte colony-stimulating factor | Recovered (respiratory symptoms improved within 3 days and patient discharged on day 15) |
| Wahlster et al. [29] | 17 Y/O male K/C of refractory chronic ITP on eltrombopag and mycophenolate mofetil | Fever, fatigue, emesis, diarrhea, progressive jaundice, marked pallor, tachycardia, tachypnea and hypoxemia | 4 days   | Evans syndrome Steroid, packed cell transfusion                           | Recovered (Hb became stable within 48 h of steroid administration)        |
| Li et al. [30]       | 39 Y/O male                         | First admission: fever, chills, dyspnea, hemoptysis, epistaxis, sore throat, productive cough, tachycardia, tachypnea and abnormal blood bilirubin, hematemesis, melena, hematocrit and no petechiae, ecchymosis or rash | About 7 days | Evans syndrome First admission: proton pump inhibitor, IVIG Second admission: IVIG | Recovered (in first admission that patient had ITP, resolution of bleeding and raise of Plt occurred on day 5 and the patient was discharged on day 6; Hb drop also responded to IVIG in second admission) |
| Vadlamudi et al. [31]| 23 Y/O female gravida 2, para 1, at 38 weeks of pregnancy in active labor | Spontaneous rupture of membranes, contractions, blood-tined discharge, history of ecchymosis and an episode of epistaxis 2 weeks prior, no pallor, ecchymosis or organomegaly On day 38 of postpartum: chest pain and shortness of breath | Not clear | Evans syndrome IV iron dextran, IVIG, rituximab, dexamethasone, packed cell and Plt transfusion | Recovered (Continued) |
| Zulfiqar et al. [9]  | 65 Y/O woman K/C of HTN and autoimmune hypothyroidism | On admission: fever, dry cough, fatigue, abdominal discomfort, tachypnea, O₂ sat: 89% On day 4: epistaxis and lower extremity purpura On day 9: right frontal headache without fever, vomiting or focal neurologic deficit 8 days | ITP 8 days | IV amoxicillin-clavulanic acid, Plt failed to raise in response to IVIG but increased in response to steroid and eltrombopag, Plt transfusion | Recovered (after administration of steroid and eltrombopag at day 9, Plt increase at day 10 and purpura resolved at day 13) |
| First author | History of the patient | Clinical presentations | Timing of the hematologic presentations | Autoimmune disorder | Treatment | Outcome |
|--------------|------------------------|------------------------|------------------------------------------|---------------------|-----------|---------|
| Revuz et al. | 1. 57 Y/O female K/C of psoriatic arthritis on adalimumab and methotrexate 2. 76 Y/O male K/C of metastatic bronchiolar adenocarcinoma on carboplatin, pemetrexed and pembrolizumab 3. 39 Y/O male with history of ITP 15 years ago | 1. Fever, tachypnea, petechiae on legs and gingival mucosa 2. Fever, slight purpura on legs 3. Fever, cough, arthralgia, body aches, unilateral epistaxis | 1. 9 days 2. The lowest Plt at day 11 3. Less than 7 days | ITP | 1. IVIG 2. IVIG 3. IVIG | 1. Recovered (Plt raised after first dose of IVIG) 2. Recovered (Plt returned to normal in 7 days) 3. Recovered (Plt raised significantly after first dose of IVIG) |
| Bennett et al. | 73 Y/O female K/C of HTN, hyperlipidemia, seasonal allergies | Fever, shortness of breath, headache, fatigue, diarrhea, generalized body aches | Less than 7 days | ITP | HCQ, dexamethasone (without response), IVIG, Plt transfusion | Recovered (Plt had marked response to treatment on day 4 and discharged on day 5) |
| Bomhof et al. | 1. 59 Y/O male K/C of small bowel stage IV neuroendocrine tumor 2. 66 Y/O female K/C of HTN 3. 67 Y/O male K/C of HTN and DM | 1. History of cough and fever 10 days before, oral petechiae and skin hematomas 2. History of fever, dyspnea, cough, diarrhea and vomiting 4 weeks ago, petechiae, epistaxis, increased hemorrhoid blood loss 3. Fever, dyspnea, cough | 1. 10 days 2. About 4 weeks 3. 21 days | ITP | 1. IVIG, dexamethasone, Plt transfusion 2. Patient did not respond to dexamethasone but responded to IVIG, Plt transfusion 3. Plt transfusion | 1. Recovered (Plt raised rapidly in response to IVIG but dropped again, then dexamethasone was administrated and significantly increased Plt) 2. Recovered (Plt raised in response to IVIG administration at day 6) 3. Deceased within 24 h of ITP occurrence (due to intracerebral bleeding) |
| Hindilerden et al. | 86 Y/O male K/C of HTN and DM | Fever, dry cough, fatigue, excessive purpuric eruptions and bruising, oral hemorrhagic bullae, tachycardia, O₂ sat: 91% | <7 days | ITP | Favipiravir, azithromycin, IVIG, prednisolone | Recovered (Plt responded to treatment and doubled in 2 days and normalized in the 3rd week) |
| Lorenzo-Villalba et al. | 1. 66 Y/O male K/C of HTN, DM & liver cirrhosis 2. 57 Y/O female K/C of HTN, thyrotoxicity & secondary hypoparathyroidism 3. 79 Y/O male K/C of HTN and a previous episode of transient recovered pancytopenia | 1. Fever, progressive shortness of breath, cough, diarrhea, tachycardia, O₂ sat: 93%, diminished Breath sounds with rales in left side, facial and trunk erythema, epistaxis 2. Fever, progressive shortness of breath, dry cough, epistaxis, cutaneous purpura on the lower extremities, oral hemorrhagic bullae, tachycardia, O₂ sat: 92%, diminished Breath sounds with rales in left side 3. Fever, dry cough, confusion, falls, cutaneous petechial purpura on the lower limbs, O₂ sat: 93%, diminished breath sound with rales in the right pulmonary base | 1. 11 days 2. 8 days 3. About 7 days | ITP | 1. IVIG, eltrombopag 2. IVIG, eltrombopag 3. No IVIG or eltrombopag | 1. Recovered (IVIG was discontinued owing to acute heart failure. Ertrombopag then initiated and after 3 days Plt increased and patient discharged on day 15) 2. Recovered (patient was discharged on day 14) 3. Recovered (spontaneously) |
| Deruelle et al. | 41 Y/O obese man K/C of HTN | Fever, dyspnea, cough, tachypnea, O₂ sat: 97% | 13 days | ITP | Steroid, IVIG | Recovered (IVIG were introduced on day 14 and Plt began rising after 3 days and then fell again on day 19. IVIG was then administered and 2 days later, Plt returned to normal) |
| Lévesque et al. | 53 Y/O male K/C of HTN, DM, dyslipidemia | Abnormal bleeding from the tracheotomy site and the left main stem bronchus during tracheotomy, no skin purpura | 20 days | ITP | Antibiotic combination, IVIG, Plt did not rise in response to high-dose dexamethasone and intravenous tranexamic acid but responded to | Recovered (the bleeding finally stopped with the high platelet transfusion support within first 5 days but Plt did not rise in response) |
| Author et al. | Age | Gender | Race | Presentation | Treatment | Recovery | Notes |
|--------------|-----|--------|------|--------------|-----------|----------|-------|
| Merli et al. [39] | 37 Y/O female | K/C of SLE and chronic ITP secondary to lupus (treated with IVIG) | | History of fever, dry cough, anosmia and fatigue 14 days ago, sudden appearance of lower extremities purpura | romiplostim and vincristine, packed cell and Plt transfusion | Not rise; Plt started to increase after 6 days of romiplostim | Recovered (Plt gradually increased and the patient was discharged on day 11) |
| Yang et al. [40] | 1. 32 Y/O female | 2. 65 Y/O female K/C of HTN and autoimmune hypothyroidism | | Fever, cough, fatigue, skin petechia mainly on lower extremities | 1. Lianhua, qingwen, oseltamivir, methylprednisolone, IVIG | 1. Recovered (not much detail on recovery course) | 2. Unknown |
| Martincic et al. [41] | 48 Y/O obese male K/C of T2DM and obstructive sleep apnea | | | Fever, progressive dyspnea, cough, headache, muscle soreness, tachycardia, tachypnea, O2 sat: 89% while receiving high flow oxygen via a non-rebreather mask, blood pressure: 163/60 | HCQ, lopinavir/ritonavir, tazocin, nadroparin, IVIG, dexamethasone, pooled Plt concentrate transfusion | Recovered (Plt normalized within 3 days and patient discharged on day 23) |
| Humbert et al. [42] | 84 Y/O male | K/C of polymyalgia rheumatica and essential tremor | | Progressively worsening dyspnea, cough, bilateral crackles on auscultation | Ceftriaxone, hydrocortisone, prednisolone, IVIG | Recovered (Plt started to increase the day following IVIG and normalized within 1 week) |
| Pedroso et al. [43] | 1. 67 Y/O female | 2. 41 Y/O female K/C of T1DM and CKD | | She was admitted due to traumatic subcapital right femur fracture and planned for surgery. In hospital course: cough, skin blood suffusions on puncture sites | 1. Plt did not respond to sole use of Plt transfusion; then, with steroid, Plt reached normal levels | 1. Recovered (Plt reached normal levels within 5 days; patient discharged on day 48) | 2. Recovered (maintained hospitalized for surveillance and spontaneous Plt recovery) |
| Nesr et al. [44] | 34 Y/O pregnant female in second trimester with a past history of ITP | | | Fever, dry cough, petechiae, gum bleeding | IVIG, prednisolone | Recovered (Plt rapidly raised on day 2 and the patient was discharged that day) |
| Metallidis et al. [45] | 33 Y/O female K/C of T1DM | | | Low-grade fever, sore throat, mild myalgias, O2 sat: 98% | IVIG, dexamethasone | Recovered (Plt rapidly raised following the treatment and patient discharged about 9 days later) |
| Tsao et al. [46] | 10 Y/O female | | | History of fatigue, non-productive cough and fever in 3 weeks ago, wet purpura in mouth, petechiae on her lower extremities, chest and neck, ecchymosis of popliteal regions and shins | IVIG, diphenhydramine, acetaminophen | Recovered (patient discharged at day 2 and had telehealth visits; rash and oral lesions improved within 48 h and Plt normalized in 2 weeks) |
| Tang et al. [47] | Pregnant female at the 41th weeks of pregnancy | 1. 94 Y/O patient K/C of HTN, chronic obstructive pulmonary disease and chronic | | Labor contractions, sore throat, O2 sat 98%, no signs of easily bruising or bleeding | IVIG, Plt transfusion | Recovered (Plt responded rapidly within 1 d) |
| | | 2. Fever, persistent cough, dyspnea, persistent cough, | | | | Recovered (All cases had a good response after initial treatment, faster |

(Continued)
| First author  | History of the patient                                      | Clinical presentations                                                                 | Timing of the hematologic presentations | Autoimmune disorder                   | Treatment                                      | Outcome                                      |
|--------------|-------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------|----------------------------------------|------------------------------------------------|-----------------------------------------------|
| de la Cruz-  | 1TP                                                         | myelopreservation of hyperlipidemia                                                      | 1. ITP relapse                         | 1. HCQ                                 |                                               | than is typically observed in other patients  |
| Benito et al.| 2. 55 Y/O patient K/C of hyperlipidemia                     | 3. Fever, dyspnea, persistent cough, myelopathy, dysgeusia                             | 2. New ITP 3.                         | 2. HCQ, IVIG                           |                                               | newly diagnosed cases. All the patients      |
|             | 3. 41 Y/O patient                                           |                                                                                        | New ITP                                | 3. Steroid                             |                                               | exhibited a Plt < 7 days)                    |
| Murt et al.  | 41 Y/O male                                                 | Cough, rhinorrhea, petechial and purpuric rash, nasal bleeding                         | 15 days                               | ITP                                    | Favipiravir, high-dose dexamethasone, IVIG     | Recovered                                     |
| Levraut et al.| 63 Y/O female K/C of autoimmune hypothyroidism and stroke | History of fever, dry cough and headaches in prior weeks, lower limb purpura, bruises of both arms and legs, bilateral ecscles at lung bases | 26 days                               | ITP                                    | IVIG                                           | Recovered                                    |
| Lobos et al. | 22 Y/O male                                                 | Petchia on extremities, gingival bleeding and buccal hematomata after a dental procedure | No symptoms of infection               | ITP                                    | IVIG, Ebtrombopag                             | Recovered (patient discharged on day 6)      |
| Kewan et al. | 89 Y/O male K/C of CHF, HTN, T2DM, CKD and AF (on warfarin) | Dyspnea, dry cough, diarrhea, cracks at lung base auscultation                        | 16 days                               | ITP                                    | HCQ, tazocin, azithromycin, IVIG, dexamethasone, Plt transfusion | Deceased (Pt responded to 2 days treatment course; patient deceased due to his poor condition) |
| Hayden et al.| 51 Y/O female K/C of long-standing SLE (18 years) and APLS, left below-knee amputation complicated by a perioperative cerebrovascular accident | Fever, 1 week hemoptysis, normal O2 sat                                                | Not mentioned                          | ITP                                    |                                               | Recovered (on day 8, the patient received first dose of etrombopag and Plt normalized in 4 days; patient discharged on day 13) |
| Molinaro et al. | 19 Y/O female                                                | Afebrile, fatigue, ageusia, normal O2 sat, diffuse purpuric lesions mostly on lower extremities | 14 days                               | ITP                                    | HCQ, anti-retroviral agents, methylprednisolone, IVIG | Recovered (Pt response initiated at day 3 and patient was discharged at day 5) |
| Mahévas et al.| 1. 58 Y/O female                                             | 1. Fever, cough, purpura, epistaxis, oral hemorrhagic bullae                           | 1. 10 days                            | 1. IVIG                                |                                               | Recovered (significant response in all patients except for patients 3, 7 and 13 that had relapse on day 38, 30 and 35, respectively) |
|             | 2. 66 Y/O male                                               | 2. Fever, cough, anemia, epistaxis                                                     | 2. 13 days                            | 2. IVIG                                |                                               |                                              |
|             | 3. 62 Y/O male                                               | 3. Fever, cough                                                                       | 3. 5 days                             | 3. IVIG                                |                                               |                                              |
|             | 4. 62 Y/O male                                               | 4. Dyspnea                                                                            | 4. 2 days                             | 4. Prednisolone                        |                                               |                                              |
|             | 5. 74 Y/O male                                               | 5. Fever, cough, purpura, mucosal bleeding, gastrointestinal bleeding                  | 5. 12 days                            | 5. Prednisolone                        |                                               |                                              |
|             | 6. 63 Y/O male                                               | 6. Fever, dyspnea                                                                     | 6. 23 days                            | 6. Prednisolone                        |                                               |                                              |
|             | 7. 65 Y/O male                                               | 7. Fever                                                                              | 7. 22 days                            | 7. Dexamethasone                       |                                               |                                              |
|             | 8. 66 Y/O female                                             | 8. Fever, dyspnea                                                                     | 8. 8 days                             | 8. Methylprednisolone, IVIG, eltrombopag |                                               |                                              |
|             | 9. 79 Y/O female                                             | 9. ITP                                                                                | 9. 16 days                            | 9. IVIG                                |                                               |                                              |
|             | 10. 59 Y/O female                                            | 10. ITP                                                                               | 10. 30 days                           | 10. IVIG                              |                                               |                                              |
|             | 11. 61 Y/O female                                            | 11. ITP                                                                               | 11. 25 days                           | 11. IVIG                              |                                               |                                              |
|             | 12. 69 Y/O female                                            | 12. IVIG                                                                              | 12. 14 days                           | 12. IVIG                              |                                               |                                              |
|             | 13. 53 Y/O male                                              | 13. IVIG                                                                              | 13. 27 days                           | 13. Prednisone                        |                                               |                                              |
|             | 14. 72 Y/O male                                              | 14. IVIG                                                                              | 14. 15 days                           | 14. Prednisolone                      |                                               |                                              |
| Pascolini et al. | 1. 69 Y/O female K/C of recently diagnosed cerebral lymphoma | 1. Admitted for pulmonary embolism while receiving chemotherapy                        | 1. 7 days                             | ITP                                    | 1. Ceftriaxone, LMWH, dexamethasone           | Recovered (All cases recovered but there is not much detail about recovery course) |
|             | 2. 88 Y/O male K/C of CHF and recent hip replacement         | 2. Flare of CHF                                                                       | 2. Not mentioned                      | 2. Methylprednisolone                  |                                               |                                              |
|             | 3. 31 Y/O male                                               | 3. Fever and dyspnea                                                                  | 3. Not mentioned                      | 3. HCQ, Ceftriaxone                    | Prednisolone, LMWH                           |                                              |
| Name et al. | Age | Gender | Symptoms | Days | Diagnosis | Treatment | Outcome |
|------------|-----|--------|----------|------|-----------|-----------|---------|
| Soares et al. | 2 Y/O female | Fever in prior weeks, bruises and petechiae throughout her body | More than 25 days | ITP | IVIG | Recovered (Plt normalized within 5 days after IVIG administration but relapsed on day 40 post-IVIG) |
| Clerici et al. | 64 Y/O male | Fever, epistaxis, mucocutaneous petechiae, wet purpura, left axillary lymphadenopathy | 3 days | ITP+ Hodgkin's lymphoma | IVIG | Recovered (Plt was unresponsive to steroids and IVIG but romiplostim administration increased Plt, Plt pool transfusions and bilateral tranexamic acid-soaked nasal tampons for epistaxis) |
| Kondo et al. | 58 Y/O female | Fever, productive cough | 2 days | ITP flare | Ciclesonide inhalation, IVIG | Recovered (Plt responded to treatment with romiplostim within 1 week) |
| Hu et al. | 72 Y/O female | Fever, dry cough, anosmia, dysgeusia | 6 days | TTP | HCQ, lopinavir/ritonavir, azithromycin, Plt did not respond to IVIG and methylprednisolone but did to plasma exchange | Recovered (Plt significantly raised within 24 h of plasma infusion) |
| Kondo et al. | 58 Y/O female | Fever, dyspnea, cough, diarrhea, headache, evidence of ischemia in the lower limbs bilaterally as well as in digits two and three of the left hand | 1. 18 days | APLS | Oseltamivir, IVIG | Not mentioned |
| Escher et al. | 72 Y/O male | Fever, shortness of breath | More than 12 days | APLS | Prophylactic dalteparin which was replaced with therapeutic dose of LMWH on day 21 | Recovered (not much detain on the recovery course) |
| Hossri et al. | 1. 29 Y/O female | Fever, non-productive cough, vomiting, abdominal pain, generalized myalgia, tachycardia, Bilateral crickles, lethargy, altered mental status, O2 sat: 99% | 1. 10 days | APLS | HCQ, tocilizumab, therapeutic heparin | Not mentioned |
| First author | History of the patient | Clinical presentations | Timing of the hematologic presentations | Autoimmune disorder | Treatment | Outcome |
|--------------|------------------------|------------------------|-----------------------------------------|---------------------|-----------|---------|
| Maria et al.  [65] | 48 Y/O male K/C of primary APLS (revealed by venous thromboembolic event) treated since 2013 with vitamin K antagonists | productive cough, tachycardia, cold left lower extremity with mild pallor and cyanosis with absent dorsalis pedis and posterior tibialis pulses; Fever, cough, myalgia, mild hypoxemia (pO₂: 75 mm Hg), O₂ sat: 96% on day 7: sudden abdominal pain (bilateral adrenal glands hemorrhage) On day 12: painful acral ischemic lesions concerning left toes (dorsalis pedis artery occlusion) | 12 days | APLS flare | HCQ and azithromycin, VKA switched for LMWH on day 7. On day 12, LMWH was replaced by IV continuous unfractionated heparin (anti-Xa) | Recovered (there was no other clinical or radiological thrombotic event occurred after administration of unfractionated heparin and patient was discharged on day 22) |
| Cardoso et al.  [66] | 18 Y/O female K/C of autism spectrum disorder and panic disorder | History of productive fever, dyspnea, cough and malaise in prior weeks, tachypnea, tachycardia, hypotension, hemodynamic collapse and respiratory failure which progressed to cardiac arrest and had a pericardial tamponade drained, severe ventricular dysfunction (EF: 20–25%) and worsening renal function with proteinuria and hematuria requiring hemodialysis, multiple DVT | More than 14 days | SLE and possible APLS | HCQ, ceftriaxone, vancomycin, azithromycin, tocilizumab, steroids, plasma exchange, anticoagulation | Deceased (plasmapheresis was discontinued due to a concern of possible removal of antibodies needed for the adaptive response to infection; patient deceased on day 17) |
| Frankel et al.  [67] | 66 Y/O female with past history of multiple abortions | Fever, dyspnea, vomiting and nausea, abdominal pain, history of one episode syncope, decreased blood pressure. Diffuse abdominal tenderness, O₂ sat: 94% | 5 days | APLS | Steroid | Recovered (patient was discharged on day 11) |

AF, atrial fibrillation; AIHA, autoimmune hemolytic anemia; APLS, antiphospholipid syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; HCQ, hydroxychloroquine; HTN, hypertension; ITP, idiopathic thrombocytopenic purpura; IV, intravenous; IVIG, intravenous immunoglobulin; K/C, known case; LMWH, low molecular weight heparin; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTP, thrombotic thrombocytopenic purpura; Y/O, year-old.
to discontinue the plasmapheresis due to their concern of possible removal of antibodies needed for the adaptive response to infection. There were no statistically significant association between the presence of age, gender, having comorbidity and timing of hematological presentation and outcome (recovered or deceased) of the study cases (all p-values were above .05). Therefore, it could be concluded that among those who the autoimmune disorder-oriented treatment was administered (93 out of 94 patients), the remission rate was 95.6% (89 out of 93 patients).

Among the patients with ITP, 15 patients received intravenous immunoglobulin (IVIG), 13 patients received steroids, 13 patients received a combination of IVIG and steroid, 6 patients received a combination of IVIG and thrombopoietin-receptor agonist (TPO-RA) and 4 patients received only supportive care including platelet cell transfusion and treatment of the underlying disorder which is the SARS-CoV-2 infection. Among the patients who started their treatment with IVIG, two patients failed to respond to IVIG (86% remission rate) and further steroid was added to their treatment regimen and then their platelet level was raised. Similarly, among those with steroid, response was not observed in two patients (84% remission rate) and IVIG was initiated for them. The majority of patients who developed AIHA were treated with supportive care (59%) and for others steroid or combination of steroid with IVIG or immunosuppressor medications was administered.

Discussion

Through our study, it was revealed that AIHA, ITP, TTP, APS, autoimmune neutropenia and Evans syndrome are among the observed hematologic autoimmune sequelae in the patients infected with SARS-CoV-2 infection. However, the exact pathogenesis from which these autoimmune sequelae are developing remains to be fully determined. Although one could label these autoimmune disorders as incidental findings in the patients with SARS-CoV-2 infection, there are a number of evidences that are in favor of the existence of a causative relationship. From a pathogenesis point of view, secondary to viral infection, immunological tolerance could be disturbed through a variety of mechanisms that include molecular mimicry, bystander activation, epitope spreading and autoreactive effector cells immortalization [8]. Several viral infections have been identified so far to be associated with hematologic autoimmune disorders such as human immunodeficiency virus, hepatitis C virus and Epstein–Barr virus [68]. Therefore, CoV infection could be attributed to trigger a cascade of both the innate and adaptive immune arms activation resulting in autoimmunity. Consistently, previous studies on other coronaviruses, SARS-CoV-2’s cousins with a high rate of similarity in their genomic sequence and receptor-binding domains, revealed that this viral family could also lead to autoimmune disorders including hematologic ones [69–71]. Furthermore, the temporal sequence of autoimmune events described in Table 1 suggests that COVID-19 could play a causal role.

The mean days between the presentations of the hematologic autoimmune disorders and the presentations of SARS-CoV-2 infection were 11.8 ± 7.1 days for the included cases. Consideration of this point could help in early suspicion of an autoimmune underlying basis in the case of deterioration of the clinical condition or when there is an abnormal hematologic index even in the COVID-19 setting (for example, in these patients, thrombocytopenia is frequently seen but very low level of platelet which led to bleeding diathesis or bleeding complications is rare [72]), especially when the event occurs in 10–13 days after the first manifestations of the infection.

A wide range of hematologic abnormalities have been observed in the patient with SARS-CoV-2 infection [73]. Among these hematologic abnormalities, a hypercoagulable state associated with thromboembolic complications and poor prognosis develops in a majority of patients [74]. However, in about one-third of patients with SARS-CoV-2 infection, mild to severe degree of thrombocytopenia is found [75]. Several possible mechanisms for thrombocytopenia in the course of CoV infection have been proposed including platelet production insufficiency rooted from classic cytokine storm in infectious diseases or direct attack on hematopoietic stem cells, increased peripheral platelet destruction and declined circulating platelet secondary to lung injury [76–78].

In most patients experiencing thrombocytopenia in the course of infection, there are no definitive data revealing increased risk of bleeding and the platelet count did not decrease to a level at which bleeding occurs [76]. A small subgroup of this thrombocytopenia is found to be immune-mediated in which the immune response had been triggered by SARS-CoV-2 infection [79]. An immune etiology should be specially considered in the setting of acute and profound decrease in the platelet count in which no other causes are found, especially those that may induce abrupt feature of thrombocytopenia. Consistently, in the ITP cases reported in Supplementary material 1, first, a series of paraclinical workups, such as viral markers, peripheral blood smear and/or bone marrow study, were done for patients with abnormally low platelet count to excluded classic causes of thrombocytopenia and then, the diagnosis of ITP was made in the case with the absence of any demonstrable primary disease [80]. For example, as a noticeable percent of patients with COVID-19 are indicated to receive anticoagulation, heparin-induced
Thrombocytopenia should always be kept in mind. It is important to take the patients’ setting into the consideration of diagnosis; in pregnant women, HELLP syndrome (hemolysis, elevated liver function tests, low platelet count) and gestational thrombocytopenia should be suspected and evaluated. Furthermore, meticulously and detailed history for potential risk factors for the emergence of ITP could help in diagnosis. A majority of cases reported to have ITP, had a risk factor including a previous ITP episode, use of immunomodulating medications, chemotherapy, etc.

Given the multiorgan involvement and multifaceted nature of SARS-CoV-2 infection and the complexity of its management, development of newly diagnosed or recurrent ITP may raise many therapeutic challenges. Besides inherent hypercoagulable state seen in most cases with COVID-19, ITP, itself and its treatment-related factors such as thrombopoietin-receptor agonists are also reported to be associated with a mild elevation in thrombotic risk [77]. Management of these coexisting conditions warrants an individualized approach to achieve a precise balance between the risk of severe bleeding and of thromboembolic events. Furthermore, there is still lack of data whether the available treatment options could interfere with the adaptive immune response against the pathogen that has already assaulted the body.

The treatment regimens for ITP target mainly whether the immune-mediated peripheral platelet destruction process or the thrombopoiesis process occurred in the bone marrow. Routinely, in most patients with ITP, the first-line treatment consists of IVIG or steroid or a combination of both [81]. Likewise, in the study cases described in Table 1, most cases received the first-line therapy and their platelet level increased in response to the treatment. About 90% of patients for whom first-line therapy was administered (40 out of 44 patients), the response was observed. Steroid treatment is the most widely used standard first-line therapy for the management of new-onset or relapsed ITP. Although steroid administration theoretically poses a higher risk of the development of viral infection and may lead to suppression of immune system [82], in the cases with ITP who received steroid, no worsening of COVID-19 course or symptoms were reported. However, further evidence with more robust methodology and design is required to fill the gap. Another concern associated with glucocorticoid use is that as seen in Table 1, most patients with ITP had an underlying disease which warranted great caution for the use of glucocorticoids including hypertension, hyperglycemia and osteoporosis, etc [83]. In these cases, it should be considered to use the minimum necessary dose and duration. Another first-line therapy for ITP is IVIG, which is more suggested for cases with very low levels of platelet and at risk for severe bleeding; many patients respond to IVIG within the first 24 h of its administration and typically the increase is observed in the platelet count in 2–4 days in those who are going to respond to IVIG while the improvement of platelet count in the course of glucocorticoids takes several days to weeks [84]. Although, first-line treatment failure was not common in the reported cases of COVID-19 with ITP (six patients who later responded to the second therapeutic regimens), it should be considered to strictly monitor the hematological indices to avoid foreseeable complications. A practical guideline by Pavord et al. [77] for the management of ITP recommends to use steroids as the first-line option with minimum dosing and duration and suggest to use IVIG in two settings: as a first-line option in those with risk for severe bleeding and as an alternative in those who failed to respond to steroids.

Studies have shown that there is a high risk of coagulopathy and thrombosis formation in patients with COVID-19 [74,85]. Although the exact mechanisms involved remain unclear, it could be assumed that expression of procoagulant and antifibrinolytic factors is attributed mostly to systemic inflammatory state, endothelial activation and hypoxia resulting in altered hemostatic balance [74]. However, an additional factor is detected in bloodstream circulation of patients with SARS-CoV-2 infection with a higher rate of activation of blood coagulation and thrombosis. This additional factor is the presence of antiphospholipid antibodies indicating an APS-like condition including lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein antibodies. In a study on 150 patients with COVID-19 hospitalized in the intensive care unit, 64 thrombotic events were observed that most of the patients with these events had positive antiphospholipid antibodies [85]. Zhang et al. [62] described three critically ill patients diagnosed with COVID-19 who developed thromboembolic events. These patients were detected to be positive for Anticardiolipin and anti-β2-glycoprotein antibodies which is indicative of a notion of APS-like phenotype in these patients.

Another hematologic autoimmune disorder seen in patients with COVID-19 is AIHA. This disorder should mainly be suspected in patients with severe anemia and those with an abrupt decrease in their hemoglobin concentration in the setting that no other attributable cause be identified. As the mainstay of treatment for AIHA, especially cold agglutinin syndrome, is the detection of the underlying cause and its specific treatment, it is important to diagnose SARS-CoV-2 infection in the asymptomatic patients and those with mild symptoms. These findings may suggest to gather samples for SARS-CoV-2 RT–PCR in all new-onset hemolytic anemia even with minor or without respiratory symptoms. In most patients with AIHA of this systematic review, the hemoglobin level stabilized in
response to supportive therapy including packed cell transfusion and the use of steroid or immunomodulators should be preserved for those with treatment failure and those warrant a rapid correction of hemodynamic status [86].

**Conclusion**

Even with confirmation of the diagnosis of hematologic autoimmune disorder in the patients, a causative relationship between SARS-CoV-2 infection and these autoimmune events still requires further studies. These systematic reviews help us gain a more comprehensive understanding of the risk of development of hematologic autoimmune disorders in infected patients; besides, it helps us always consider an autoimmune etiology for cases with abnormal hematologic findings which further led to an appropriate treatment of the patients, especially when the symptoms present in about 1–2 weeks after the first manifestation of the infection symptoms. With this in mind, the doctor will constantly monitor the patient and consider the likelihood of such events occurring. This will result in the prompt physician’s clinical suspicion when the early manifestations of the autoimmune disorders of the patient appear. Maybe, at least in this SARS-CoV-2 pandemic, it should be recommended to evaluate patients with an unexpected and unexplained decrease in their hemoglobin or platelet count for SARS-CoV-2 infection. Another challenging issue in this field is treatment regimens for ITP. Based on the literature, it is suggested that, in overall, steroids be used as the first line of therapy if there are no contraindications; however, given the multiorgan involvement and multifaceted nature of SARS-CoV-2 infection, an individualized approach should be taken for each patient.

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