Respiratory Medicine Case Reports 34 (2021) 101563

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Delayed onset of severe immune thrombocytopenia associated with COVID-19 pneumonia

Shintaro Sato [a,*], Moegi Kurachi [b], Hiroki Ohta [a], Tomohiko Nakamura [a], Tomohiro Oba [a], Rie Kawabe [a], Hideaki Yamakawa [a], Masako Amano [a], Hidekazu Matsushima [a]

[a] Department of Respiratory Medicine, Saitama Red Cross Hospital, Saitama, Japan
[b] Department of Hematology, Saitama Red Cross Hospital, Saitama, Japan

ARTICLE INFO

Keywords:
COVID-19
Diffuse alveolar hemorrhage
Immune thrombocytopenia
Purpura

ABSTRACT

A 72-year-old Japanese man was admitted to our hospital for treatment of severe COVID-19 pneumonia and was started on favipiravir, heparin calcium, and methylprednisolone pulse therapy. He recovered from respiratory failure about one month later. However, he soon developed purpura in his lower limbs and thrombocytopenia, and immune thrombocytopenia was subsequently diagnosed. Although immune thrombocytopenia is one of the early complications of COVID-19, the use of corticosteroids for COVID-19 is thought to be a factor in the late onset of immune thrombocytopenia. In cases of severe COVID-19 for which corticosteroids were used for treatment, autoimmune diseases such as immune thrombocytopenia may manifest themselves late in the disease course.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by infection from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As of May 2021, more than 160 million confirmed cases and 3.3 million deaths have been reported [1]. COVID-19 is known to cause a variety of extrapulmonary manifestations, although the primary target of SARS-CoV-2 is the respiratory tract [2]. Among these extrapulmonary manifestations, hematologic abnormalities such as deep vein thrombosis, pulmonary embolism, and arterial thrombosis account for most of the hematologic manifestations, and there are limited reports of autoimmune hematologic abnormalities [3]. We present a case of delayed onset of severe immune thrombocytopenia associated with severe COVID-19 pneumonia.

2. Case presentation

A 72-year-old Japanese man with well-controlled hypertension presented to his local physician 7 days prior to admission for cough and shortness of breath, and a reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 via nasopharyngeal swab was positive. He was admitted to a nearby hospital and received oxygen therapy but was referred to our hospital due to deterioration of

Abbreviations: COVID, coronavirus disease 2019; DAH, diffuse alveolar hemorrhage; HD, hospital day; HFNC, high-flow nasal cannula; IVIG, intravenous immunoglobulin; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

* Corresponding author. Department of Respiratory Medicine, Saitama Red Cross Hospital, 1-5 Shintoshin, Chuo-ku, Saitama, 330-8553, Japan.
E-mail address: smallerss@hotmail.com (S. Sato).

https://doi.org/10.1016/j.rmcr.2021.101563
Received 25 July 2021; Received in revised form 17 November 2021; Accepted 28 November 2021
Available online 2 December 2021

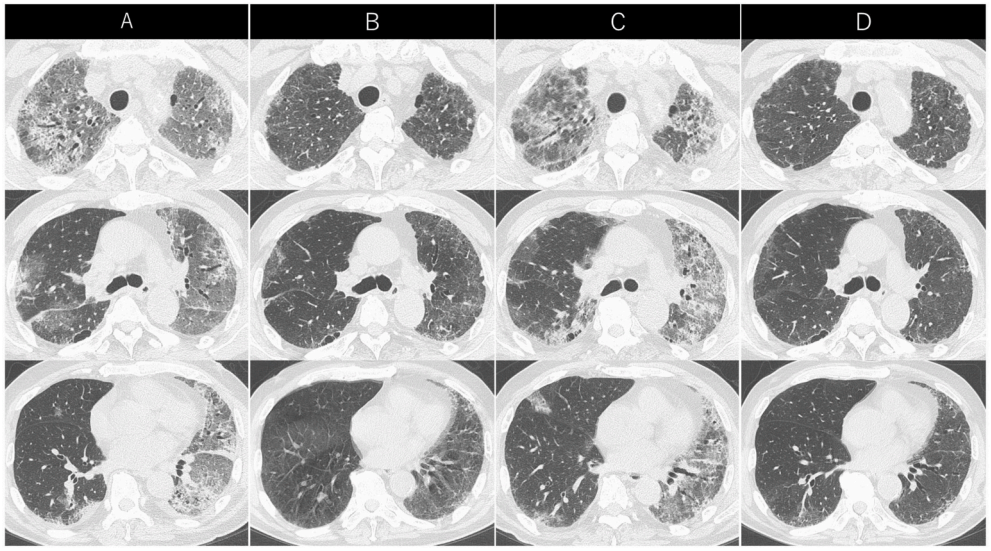

Fig. 1. Chest high-resolution computed tomography (HRCT) images of the upper and lower lobes. (A) On the day of admission, extensive ground-glass opacities and consolidation were seen predominantly in the left lung, and traction bronchiectasis and volume reduction were also present. (B) On the 26th hospital day, antiviral therapy and corticosteroid treatment including two rounds of steroid pulse therapy resulted in a marked reduction of ground-glass opacities and consolidation although reticular shadows indicative of fibrotic changes were still present. (C) On the 39th hospital day, ground-glass opacities and consolidation reappeared in the bilateral lungs superimposed on reticular shadows indicating residual fibrotic change after COVID-19 pneumonia along with hemoptysis, purpura, and thrombocytopenia. A diagnosis of diffuse alveolar hemorrhage was made by bronchoalveolar lavage after the patient was intubated. (D) On the 51st hospital day, HRCT findings improved markedly with the increase in corticosteroid dosage.

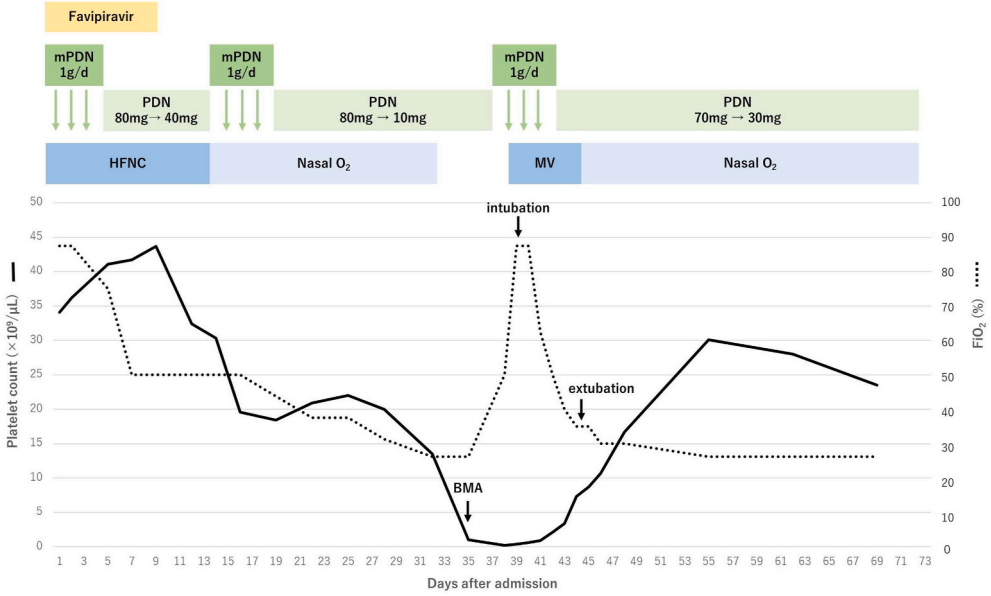

Fig. 2. Timeline of platelet counts in the 72-year-old male patient with immune thrombocytopenia during treatment of COVID-19 pneumonia. BMA, bone marrow aspiration; HFNC, high-flow nasal cannula; mPDN, methylprednisolone; MV, mechanical ventilation; PDN, prednisolone.

his general condition and respiratory status.

On admission, he complained primarily of progressive dyspnea, cough, and fever at its highest of 38.5 °C. Vital signs included a pulse rate of 62 beats per minute, blood pressure of 148/86 mmHg, body temperature of 36.6 °C, respiratory rate of 16 breaths per minute, and O_2 saturation of 90% on O_2 at 5 L/min via mask. Chest auscultation revealed fine crackles across the bilateral lung fields. Chest X-ray revealed diffuse bilateral consolidations, and high-resolution computed tomography (HRCT) revealed extensive ground-glass opacities, consolidation with traction bronchiectasis, and volume reduction predominantly in the left lung (Fig. 1A). Laboratory tests showed a hemoglobin concentration of 118 g/L (normal range 130–170), white blood cell count of 12.6 × 10^9/L (4.0–9.0),

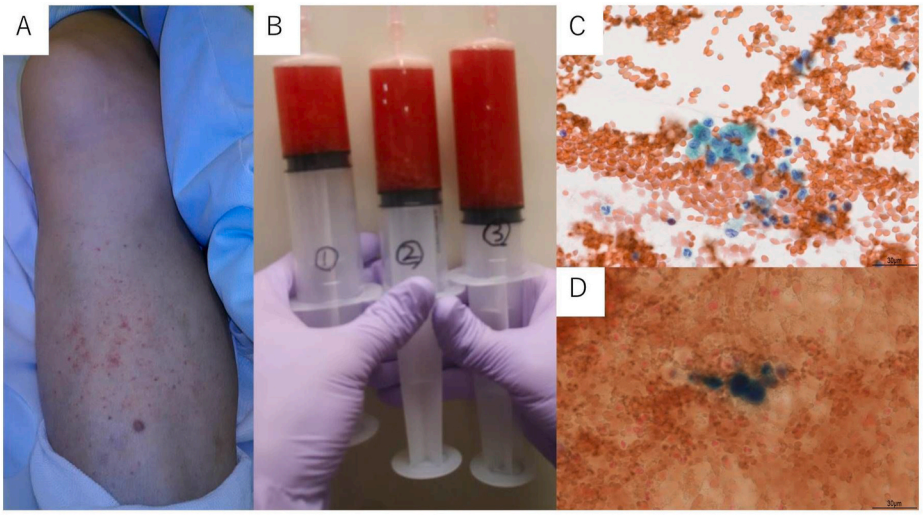

Fig. 3. (A) Purpuric lesions on the patient's lower extremity. (B) Bronchoalveolar lavage fluid from the left B^3 bronchus had a sanguineous appearance. (C) Cytological examination of the bronchoalveolar lavage fluid revealed histiocytes and neutrophils against a background of bleeding components (Papanicolaou stain) and (D) hemosiderin contained in alveolar macrophages (iron stain).

lymphopenia of 0.5×10^9/L (1.0–4.0), platelet count of 34.1×10^9/μL (15.0–40.0), C-reactive protein of 17.0 mg/dL (<0.3), ferritin of 972 ng/mL (39.4–340), and D-dimer of 3.5 μL/mL (<1.0). We diagnosed the patient as having a severe case of COVID-19 pneumonia. Treatment was begun with high-flow nasal cannula (HFNC) for his respiratory failure and favipiravir 3600 mg/day on the 1st day, followed by 1600 mg/day, piperacillin/tazobactam 13.5 g/day, azithromycin 500 mg/day, heparin calcium 10,000 U/day, and methylprednisolone pulse therapy (Fig. 2). Severe respiratory failure requiring the use of HFNC continued for approximately two weeks after admission, during which two courses of high-dose intravenous pulse therapy were administered. HRCT on the 26th hospital day (HD) showed significant improvement in the ground-glass opacities and consolidation although reticular shadows indicative of fibrotic changes remained, and he was weaned from oxygen therapy on the 32nd HD (Figs. 1B and 2).

On the 35th HD, epistaxis and purpura on his lower limbs suddenly appeared (Fig. 3A), and a complete blood count revealed isolated thrombocytopenia with a platelet count of 1.0×10^9/μL that further declined to 0.2×10^9/μL on the 38th HD (Fig. 2). The patient's coagulation times and fibrinogen level were normal, and there were no signs of hemolysis or microangiopathy on laboratory tests. Heparin-induced thrombocytopenia antibodies and testing for HBV, HCV, HIV, and CMV were negative. Antineutrophil cytoplasmic antibodies and connective tissue disease-related autoantibodies were also negative. Bone marrow aspiration revealed hypocellular marrow with megakaryocyte hyperplasia. On the 39th HD, his respiratory condition rapidly deteriorated with the occurrence of hemoptysis, and HRCT showed the new appearance of extensive ground-glass opacities superimposed on reticular shadows indicative of residual fibrotic changes such as those seen after COVID-19 pneumonia (Fig. 1C). HRCT findings were similar to those at the onset of his COVID pneumonia, but RT-PCR testing for SARS-CoV-2 was negative. We transferred the patient to the intensive care unit for mechanical ventilatory treatment, and bronchoscopy was performed after endotracheal intubation. Bronchoalveolar lavage in the left B^3c showed increasingly hemorrhagic returns with a 74% recovery rate (Fig. 3B). The fluid contained 2.8×10^5 cells/mL consisting of 56.2% macrophages, 3.0% lymphocytes, 40.4% neutrophils, and 0.2% eosinophils and was negative for microorganisms including that by *Pneumocystis jirovecii* PCR. Cytological examination of the bronchoalveolar lavage fluid revealed a significant hemorrhagic component and hemosiderin-containing alveolar macrophages stained with iron (Fig. 3C and D). Based on these findings, a diagnosis of immune thrombocytopenia complicated with diffuse alveolar hemorrhage (DAH) associated with COVID-19 was made, and we started methylprednisolone pulse therapy. On the 43rd HD, the patient's platelet count recovered to 3.4×10^9/μL without the administration of intravenous immunoglobulin (IVIG), and the patient was extubated after 5 days of mechanical ventilation. Corticosteroids were tapered from 70 mg/day (1 mg/kg) of prednisolone to 10 mg/day every other week (Fig. 2). The patient's HRCT findings had generally improved by the 52nd HD (Fig. 1D), and he was discharged on the 73rd HD after undergoing rehabilitation.

3. Discussion

We gained two important clinical insights from this case. The first is that treatment including that with corticosteroids for COVID-19 pneumonia may lead to the delayed onset of immune thrombocytopenia. The second is that lung fibrosis caused by COVID-19 may predispose patients to DAH.

The use of corticosteroids may delay the onset of immune thrombocytopenia associated with COVID-19. Immune thrombocytopenia is secondarily manifested by autoimmune and lymphoproliferative disorders and infectious diseases (e.g., *Helicobacter pylori*, human immunodeficiency virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, and varicella zoster virus) [4]. In addition to these viral infections, the recent pandemic of SARS-CoV-2 has also been found to be one of the causes of immune thrombocytopenia [3]. The pathophysiology of thrombocytopenia includes activation of T cells due to viral infection, modification of host immune

Table 1
Reported cases of COVID-19 pneumonia with severe immune thrombocytopenia.

Author	Age /Sex	Severity of COVID-19 pneumonia[a]	CS	Heparin	Time from COVID-19 onset to immune thrombocytopenia diagnosis	Severity of immune thrombocytopenia[b]	Treatment of immune thrombocytopenia	Outcome
Martincic [10]	48/ M	critical	unused	used	12days	severe (gastrointestinal bleeding)	CS, IVIG	Alive
Deruelle [11]	41/ M	critical	unused	used	27days	severe (tracheal hemorrhage)	CS, IVIG	Alive
Levesque [12]	53/ M	critical	unused	used	27days	severe (intracranial bleeding)	CS, IVIG, PT romiplostim、vincristine	Alive
Zulfigar [13]	65/ F	severe	unused	used	4days	severe (intracranial bleeding)	CS, IVIG, PT	N.D.
Bomhof [14]	67/ M	critical	unused	used	21days	severe (intracranial bleeding)	PT	Dead
Mahevas [15]	74/ M	severe	N.D.	N.D.	12days	severe (gastrointestinal bleeding)	CS	Alive
Mahevas [15]	66/ F	severe	N.D.	N.D.	8days	severe (intracranial bleeding)	CS, IVIG, eltrombopag	Alive
Our case	72/ M	severe	used	used	47days	severe (diffuse alveolar hemorrhage)	CS	Alive

CS, corticosteroid; PT, platelet transfusion; IVIG, intravenous immunoglobulin.
[a] Severity of COVID-19 is based on NIH COVID-19 treatment guidelines.
[b] Severity of immune thrombocytopenia is based onan international working group report of immune thrombocytopenic purpura of adults.

function by cytokine release, and cross-reactions of antiviral antibodies with glycoproteins such as GP IIb/IIIA and GP Ib/IX expressed on platelets and megakaryocytes [5]. Furthermore, heparin, azithromycin, chloroquine, hemodialysis, and extra-corporeal membrane oxygenation used in the treatment of COVID-19 may also be triggers for the onset of the disease [6,7]. In the latest systematic review, the mean number of days from the onset of COVID-19 to the diagnosis of immune thrombocytopenia was reported to be 13.3 ± 7.3 days [3]. In our patient, 47 days had elapsed between the onset of COVID-19 and the diagnosis of immune thrombocytopenia, and, to our knowledge, such a late onset of immune thrombocytopenia has not been previously reported. The platelet count of our patient increased after methylprednisolone pulse therapy, but it clearly decreased with the subsequent tapering of corticosteroids (Fig. 2). Therefore, we speculate that the immune thrombocytopenia may have become apparent as the corticosteroids were tapered off following improvement of COVID-19 pneumonia and that it had initially been suppressed by corticosteroids for some time after hospitalization. Corticosteroids are effective in reducing mortality and the rate of mechanical ventilation in severe COVID-19 [8], and recent guidelines recommend corticosteroids treatment for 10 days or until discharge for patients with severe or critical COVID-19 [9]. In patients with COVID-19 treated with corticosteroids or those who used corticosteroids for an autoimmune disease, it may be necessary to monitor coagulation functions for some time after COVID-19 treatment ends (Table 1).

To understand the characteristics of severe immune thrombocytopenia associated with COVID-19 that requires therapeutic intervention, we summarized the previously reported cases in the Table 1 [10–16]. Clinicians need to be cautious when discussing immune thrombocytopenia based on its severity because methods to assess immune thrombocytopenia-specific bleeding have not yet been validated in large prospective studies, and a system for classifying the severity of adult immune thrombocytopenia is not yet established [16]. An international working group has proposed that severe immune thrombocytopenia should be defined as bleeding that is clinically relevant and requires therapeutic intervention [16], and we used this definition in this report. As shown in the table, 8 patients with a mean age of 60.7 years have been reported, and the severity of COVID-19 pneumonia as classified by the World Health Organization was critical in 4 patients and severe in the other 4 [17]. Corticosteroids were used as a therapeutic agent for COVID-19 in only one patient, whereas heparin was used in 6 patients. Low-molecular-weight heparin is the only anticoagulant recommended for the treatment of coagulation abnormalities associated with COVID-19 [18]. We think that the effect of heparin on internal bleeding in immune thrombocytopenia is assumed to be small because most of the bleeding during heparin use in COVID-19 patients occurs intramuscularly [19]. The mean number of days from the onset of COVID-19 to the diagnosis of immune thrombocytopenia was 19.7 ± 13.9 days, and this tended to be longer than the number of days reported in the systematic review cited earlier (13.3 ± 7.3 days) [3]. Therefore, in patients with severe or critical COVID-19, clinicians should be alert to the development of immune thrombocytopenia for up to 4 or 5 weeks after the onset of COVID-19.

The incidence of DAH associated with immune thrombocytopenia is rare, and only a few cases have been reported [20]. To our knowledge, the present patient is the first to show DAH in immune thrombocytopenia associated with COVID-19. Several factors may have led to the development of DAH in this patient. First, the lung damage caused by COVID-19 may have resulted in tissue fragility leading to easy bleeding. The pulmonary pathology of COVID-19 shows diffuse damage to alveolar and vascular epithelium, which is often permanent [21]. In our patient, the extent of the lesions shown on chest CT at the onset of COVID-19 and with DAH were similar (Fig. 1A, C), suggesting that the site of lung injury caused by COVID-19 may have been predisposed to alveolar hemorrhage at the occurrence of immune thrombocytopenia. Nagaharu et al. pointed out that DAH can occur in COVID-19-negative immune thrombocytopenia due to underlying respiratory disease [20]. The second factor is the effect of corticosteroids used in COVID-19 treatment.

Unlike the other reported patients, our patient was the only one in whom corticosteroids were used to treat COVID-19 (Table), and we cannot rule out the possibility that corticosteroids may have prolonged the healing process of lung injury.

In the treatment of severe immune thrombocytopenia in these patients, most responded to corticosteroids and IVIG, but 2 patients had a refractory course requiring drugs such as romiplostim, vincristine, and eltrombopag in addition to corticosteroids and IVIG. Practical guidance from the British Society of Haematology recommends corticosteroids as first-line treatment and IVIG as second line treatment for COVID-19-positive immune thrombocytopenia. However, thrombopoietin receptor agonists and platelet transfusions should be avoided because of the risk of increased thrombosis, as should immunosuppressive drugs including rituximab because their impact on COVID-19 is still unclear [22]. Of these reported patients, one patient who received only platelet transfusion died, but all of the patients treated with corticosteroids or IVIG survived, indicating that even severe immune thrombocytopenia is likely to respond to standard therapy.

In conclusion, we experienced a case of delayed-onset immune thrombocytopenia associated with COVID-19 pneumonia. Because of the possibility of the delayed development of thrombocytopenia in patients after treatment of COVID-19 with corticosteroid-containing drugs, they should be followed up for a certain period of time. In addition, residual fibrotic changes in the lung due to COVID-19 pneumonia may be associated with complications of DAH in patients with immune thrombocytopenia.

Declaration of competing interest

The authors declare no Conflicts of Interest (COI) in association with this article.

References

[1] (Retrieved on June 25, 2021), https://covid19.who.int/.
[2] A. Gupta, M.V. Madhavan, K. Sehgal, et al., Extrapulmonary manifestations of COVID-19, Nat. Med. 7 (2020) 1017–1032.
[3] E. Taherifard, E. Taherifard, H. Movahed, et al., Hematologic autoimmune disorders in the course of COVID-19: a systematic review of reported cases, Hematology 26 (2021) 225–239.
[4] D.B. Cines, H. Liebman, R. Stasi, Pathobiology of secondary immune thrombocytopenia, Semin. Hematol. 46 (2009) S2–S14.
[5] S. Audia, M. Mahévas, M. Samson, et al., Pathogenesis of immune thrombocytopenia, Autoimmun. Rev. 16 (2017) 620–632.
[6] Y. Liu, W. Sun, Y. Guo, et al., Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study, Platelets 31 (2020) 490–496.
[7] S. Pavord, J. Thachil, B.J. Hunt, et al., Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic, Br. J. Haematol. 189 (2020) 1038–1043.
[8] Y.S. Pulakurthi, J.M. Pederson, K. Saravu, et al., Corticosteroid therapy for COVID-19: a systematic review and meta-analysis of randomized controlled trials, Medicine (Baltim.) 100 (2021), e25719.
[9] Retrieved on July 25, 2021), https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
[10] Z. Martincic, B. Skopec, K. Rener, et al., Severe immune thrombocytopenia in a critically ill COVID-19 patient, Int. J. Infect. Dis. 99 (2020) 269–271.
[11] E. Deruelle, O. Ben Hadj Salem, S. Sep Hieng, et al., Immune thrombocytopenia in a patient with COVID-19, Int. J. Hematol. 112 (2020) 883–888.
[12] V. Lévesque, Millaire É, D. Corsilli, et al., Severe immune thrombocytopenic purpura in critical COVID-19, Int. J. Hematol. 112 (2020) 746–750.
[13] A.A. Zulfiqar, N. Lorenzo-Villalba, P. Hassler, et al., Immune thrombocytopenic purpura in a patient with covid-19, N. Engl. J. Med. 30 (2020) e43.
[14] G. Bomhof, P.G.N.J. Mutsaers, F.W.G. Leebeek, et al., COVID-19-associated immune thrombocytopenia, Br. J. Haematol. 190 (2020) e61–e64.
[15] M. Mahévas, G. Moulis, E. Andres, et al., Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: a French multicentre series, Br. J. Haematol. 190 (2020) e224–e229.
[16] F. Rodeghiero, R. Stasi, T. Gernsheimer, et al., Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group, Blood 113 (2009) 2386–2393.
[17] WHO, Clinical management of covid-19—interim guidance, Retrieved on July 25, 2021, https://www.who.int/publications/i/item/clinical-management-of-covid-19.
[18] J. Thachil, N. Tang, S. Gando, et al., ISTH interim guidance on recognition and management of coagulopathy in COVID-19, J. Thromb. Haemostasis 18 (2020) 1023–1026.
[19] P. Lucatelli, G. De Rubeis, M. Citone, et al., Heparin-related major bleeding in covid-19-positive patient: perspective from the outbreak, Cardiovasc. Intervent. Radiol. 43 (2020) 1216–1217.
[20] K. Nagaharu, M. Masuya, K. Kawakami, et al., Successful management of immune thrombocytopenia presenting with lethal alveolar hemorrhage, Case Rep Hematol (2019) 5170282.
[21] S.S. Batah, A.T. Fabro, Pulmonary pathology of ARDS in COVID-19: a pathological review for clinicians, Respir. Med. (2021) 106239.
[22] S. Pavord, J. Thachil, B.J. Hunt, et al., Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic, Br. J. Haematol. 189 (2020) 1038–1043.