Letter to the Editor

Simon Michaelis*, Angelika Pichler, Ingeborg Stelzer, Christoph Tinchon and Dietmar Enko

Concomitant immune thrombocytopenia and bone marrow hemophagocytosis in a patient with SARS-CoV-2

<https://doi.org/10.1515/cclm-2021-0169>

Received February 5, 2021; accepted March 9, 2021;

published online March 16, 2021

Keywords: bone marrow; hemophagocytosis; SARS-CoV-2; thrombocytopenia.

To the Editor,

The ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is challenging the public and particularly health care professionals throughout the world. A diversity of clinical presentations in SARS-CoV-2 positive patients has been observed. Among a variety of underlying pathophysiological features, immune dysregulation and perturbances in blood coagulation are playing an important role in promoting more severe courses of the infection [1]. Here, we present a case of immune thrombocytopenia (ITP) and prominent bone marrow hemophagocytosis in a patient infected with SARS-CoV-2.

A 78-year-old, SARS-CoV-2 positive female patient was hospitalized at our department of hemato-oncology with a platelet-count of 5 (reference range: $140\text{--}440$) $\times 10^9/\text{L}$. She had been diagnosed with SARS-CoV-2 and pneumonia five weeks prior to that in another hospital. Symptoms of cough and dyspnea had resolved after several days with no need of intensive care. Thrombocytopenia had been found with a count of 4 ($160\text{--}370$) $\times 10^9/\text{L}$. There had been petechiae and

one episode of epistaxis. She had developed a marked increase of ferritin with a peak of $2,888$ ($13\text{--}150$) $\mu\text{g}/\text{L}$ and a slight elevation of C-reactive protein (CRP) up to 27 ($0\text{--}5$) mg/L . Thrombocytopenia had been treated with $1\text{ mg}/\text{kg}$ prednisolone and high dose immunoglobulins for seven days with a minor response (no further bleeding symptoms and temporary rise of platelets). The patient had been discharged without symptoms on prednisolone $1\text{ mg}/\text{kg}$.

On admission in our hospital the patient showed no signs of respiratory impairment, renal dysfunction or bleeding. There was no splenomegaly or an enlargement of lymph nodes. The leukocyte count was 11.44 ($3.90\text{--}10.40$) $\times 10^9/\text{L}$ with a marked decrease of lymphocytes to 0.13 ($1.10\text{--}3.60$) $\times 10^9/\text{L}$. The lymphopenia was caused by a reduction of all lymphocyte fractions. The relative decrease of T cells and natural killer cells was more pronounced compared to B cells. Hemoglobin (Hb) was 116 ($116\text{--}155$) g/L and further decreased over the clinical course to a minimum of $89\text{ g}/\text{L}$. In the peripheral blood smear atypical, presumably reactive, lymphocytes with basophilic cytoplasm and eccentric nuclei were found. Polychromasia and anisocytosis of the erythrocytes were present, but no schistocytes were detected. The size of the platelets was variable. Partially, giant platelets were found. There were no signs of dysplasia. Reticulocytes were 248 ($27\text{--}95$) $\times 10^9/\text{L}$, haptoglobin 0.12 ($0.3\text{--}2.0$) g/L and lactate dehydrogenase (LDH) 379 ($0\text{--}250$) U/L , indicating hemolysis. However, the direct Coombs test (DCT) was negative. Furthermore, ferritin levels were elevated with a peak of $1,238$ ($30\text{--}150$) $\mu\text{g}/\text{L}$. CRP, procalcitonin (PCT) and fibrinogen were normal. Interleukin-6 (IL-6) was slightly elevated with 41.8 ($0.0\text{--}7.0$) ng/L .

In our laboratory SARS-CoV-2 polymerase chain reaction showed a prolonged positivity indicated by a positive result five weeks after the first reported positive test. The ensuing tests showed alternating positive and negative results, with the last one being positive about seven weeks after the diagnosis.

Diagnostic workup for thrombocytopenia was performed. Infections with human immunodeficiency virus (HIV),

*Corresponding author: Simon Michaelis, MD, Institute of Clinical Chemistry and Laboratory Medicine, General Hospital Hochsteiermark, Vordernberger Str. 42, 8700 Leoben, Austria, Phone: +43 3842 401 3529, E-mail: simon.michaelis@kages.at

Angelika Pichler and Christoph Tinchon, Department of Hemato-Oncology, General Hospital Hochsteiermark, Leoben, Austria

Ingeborg Stelzer, Institute of Clinical Chemistry and Laboratory Medicine, General Hospital Hochsteiermark, Leoben, Austria

Dietmar Enko, Institute of Clinical Chemistry and Laboratory Medicine, General Hospital Hochsteiermark, Leoben, Austria; and Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria

hepatitis C virus (HCV), hepatitis B virus (HBV), Epstein-Barr virus (EBV) and parvovirus B19 were excluded. Antinuclear antibody (ANA) screening was negative and the ADAMTS13-activity was normal. There were no signs of disseminated intravascular coagulopathy. Functional analysis of anti-platelet antibodies showed no conclusive result. A bone marrow aspiration with cytological and flow-cytometrical analyses was performed. No signs of lymphoma or other systemic hematological disorders could be found. Bone marrow cytology showed megakaryocytic hypocellularity. Several micromegakaryocytes and hypolobulated forms, comprising less than 10% of all megakaryocytes, were detected. In the myeloid and erythropoietic cell lines, no dysplastic features were observed. Numerous prominent hemophagocytes, which engulfed myelopoietic cells, were detected (Figure 1). This cell type was present in all slides and contained intact and decomposed hematopoietic cells (e.g., erythroblasts, granulocytic forms and megakaryocytes). After a

thorough synopsis of all relevant clinical and laboratory data, the patient was diagnosed with ITP and concomitant bone marrow hemophagocytosis.

In general, ITP is characterized by low platelet counts mainly induced by anti-platelet antibodies and T-cell dependent mechanisms [2]. Viral infection (e.g., HBV, HCV, EBV or cytomegalovirus [CMV]) is a common trigger of this clinical condition [2]. ITP is diagnosed by exclusion of other possible causes of thrombocytopenia. In 50–60% anti-platelet-antibodies may be detected by functional assays, like monoclonal antibody-specific immobilization of platelet antigens (MAIPA) [1]. In our patient, no conclusive result was achievable, possibly due to interference with previous intravenous immunoglobulin (IVIG) therapy. The bleeding risk tends to be lower compared to thrombocytopenia caused by other conditions. The first line treatment consists of glucocorticoids and/or IVIG. In the case of steroid-refractory disease thrombopoietin (TPO)-agonists are the treatment of choice [2].

In the present case, ITP was accompanied by bone marrow hemophagocytosis. Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a severe clinical condition characterized by a massive production of proinflammatory cytokines (cytokine storm) accompanied by cytopenia, hyperferritinemia and fever. It can lead to multi-organ failure and eventually death [3]. Primary HLH is caused by genetic mutations and typically occurs during childhood. Secondary forms are triggered mainly by neoplasms, autoimmune disorders or infections [3]. For diagnostic purposes, the HScore has been developed. It comprises nine parameters (e.g., known immunosuppression, body temperature, organomegaly, cytopenias, ferritin, triglycerides, fibrinogen, glutamic oxaloacetic transaminase and hemophagocytes in bone marrow aspirates). Using a freely available online tool, the numerical score and the probability of suffering from this disorder can be calculated [4]. In the present case, HLH was ruled out due to absent relevant clinical and laboratory markers. CRP and PCT were only slightly increased and there was no episode of fever. Hyperferritinemia was observed, but in its range not sensitive or specific enough to indicate HLH. Nevertheless, there have been reports of HLH or at least bone marrow hemophagocytosis in patients with SARS-CoV-2 infection. In those cases, the degree of proinflammatory systemic reactions was variable. In fact, most of them lacked some of the essential features of HLH, highlighting the complex and diverse pathophysiological traits of SARS-CoV-2 (Table 1) [5–8].

The cause of hemolytic anemia remained not fully elucidated. Evans syndrome, a disorder characterized by ITP and concomitant autoimmune hemolysis, has been

Figure 1: Hemophagocytes in bone marrow aspirate. (A) May-Grünwald-Giemsa staining. (B) Prussian-Blue staining.

Table 1: Key clinical and laboratory markers of patients with SARS-CoV-2 infection and bone marrow hemophagocytosis [5–8].

Publication	Tholin et al. [5]	Debliquis et al. [6]			Lima et al. [7]	Dewaele et al. [8]	This case
		Patient 1	Patient 2	Patient 3			
Age, years	~70	78	67	63	60	55	78
Gender	m	m	f	m	f	f	f
Hemoglobin, g/L	111	124	104	85	67	68	89
Thrombocytes, $\times 10^9/L$	95	<5	26	89	161	23	4
Lymphocytes, $\times 10^9/L$	1.6	0.8	1.77	0.95	n/a	n/a	0.13
Organomegaly	No	No	No	No	n/a	n/a	No
Fever	Yes	No	No	Yes	Yes	Yes	No
Ferritin, $\mu g/L$	75,920	624	620	4,899	6,180	19,558	2,888
CRP, mg/L	348	12	204	357	262	n/a	27
LDH, U/L	1,559	219	584	588	1,123	n/a	379

CRP, C-reactive protein; LDH, lactate dehydrogenase; n/a, not applicable; m, male; f, female.

described in SARS-CoV-2 patients but was ruled out in our patient due to a negative DCT [9]. One explanation for hemolysis observed here could be the activity of hemophagocytes in the bone marrow.

After excluding other causes of low platelet count, we considered thrombocytopenia as driven mainly by an immune reaction against platelets presumably triggered by the infection with SARS-CoV-2. Multiple reports suggest that ITP is a rare but not uncommon finding in SARS-CoV-2 patients [10]. However, hypocellularity of the megakaryocytic cell line and marked hemophagocytosis as seen in the bone marrow of our patient are not typical features of ITP. Therefore, we concluded, that a bone marrow process was contributing to thrombocytopenia, either by antibodies against megakaryocytes or by the described hemophagocytosis. The emphasis seemed to be on peripheral consumption of platelets, since the extent of megakaryocytic hypocellularity was not explaining the massive drop of platelets. The contribution of different mechanisms to thrombocytopenia in SARS-CoV-2-infected patients has been described [11]. Those comprise direct impairment of hematopoietic cells, low TPO production and increased peripheral clearance of platelets [11].

In our hospital, the TPO-agonist eltrombopag was started as second-line therapy. After five weeks of treatment the platelet count was $50 (140\text{--}440) \times 10^9/L$, after seven weeks it increased to $226 (140\text{--}440) \times 10^9/L$. Thrombocytopenia has been described as risk factor for increased severity and mortality in patients infected with SARS-CoV-2 [12]. Nevertheless, our patient showed a mild course of disease and good outcome.

This case adds one more example of the variability of pathophysiological mechanisms and clinical presentations observed in patients with SARS-CoV-2. If thrombocytopenia

occurs in this patient setting, a very thorough diagnostic approach is necessary, since many different factors with different therapeutic consequences can play a role in this certain state.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' Institutional Review Board.

References

1. Ou M, Zhu J, Ji P, Li H, Zhong Z, Li B, et al. Risk factors of severe cases with COVID-19: a meta-analysis. *Epidemiol Infect* 2020;148: e175.
2. Cooper N, Ghanima W. Immune thrombocytopenia. *N Engl J Med* 2019;381:945–55.
3. Soy M, Atagündüz P, Atagündüz I, Sucak GT. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. *Rheumatol Int* 2021;41:7–18.
4. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheum* 2014;66:2613–20.
5. Tholin B, Hauge MT, Aukrust P, Fehrle L, Tvedt TH. Hemophagocytic lymphohistiocytosis in a patient with COVID-19 treated with tocilizumab: a case report. *J Med Case Rep* 2020;14:187.

6. Deblquis A, Harzallah I, Mootien JY, Poidevin A, Labro G, Mejri A, et al. Haemophagocytosis in bone marrow aspirates in patients with COVID-19. *Br J Haematol* 2020;190:e70–3.
7. Lima R, Filho CC, Ferreira Filho CM, Vaisman M, Cossenza A, Rebello CP, et al. Hemophagocytic syndrome and COVID-19. *Respir Med Case Rep* 2020;31:101162.
8. Dewaele K, Claeys R. Hemophagocytic lymphohistiocytosis in SARS-CoV-2 infection. *Blood* 2020;135:2323.
9. Li M, Nguyen CB, Yeung Z, Sanchez K, Rosen D, Bushan S. Evans syndrome in a patient with COVID-19. *Br J Haematol* 2020;190:e59–61.
10. Bhattacharjee S, Banerjee M. Immune thrombocytopenia secondary to COVID-19: a systematic review. *SN Compr Clin Med* 2020;19:1–11.
11. Zhang Y, Zeng X, Jiao Y, Li Z, Liu Q, Ye J, et al. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. *Thromb Res* 2020;193:110–5.
12. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020;506:145–8.