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QUANTITATIVE PLATELETS CHANGES DURING DIFFERENT PERIODS OF COVID-19

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Abstract

Introduction. Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. Patients who are older or have multiple risk factors or comorbidities have an increased risk of developing severe illness. We have used the following clinical definitions for the initial illness and long COVID at different times according to NICE recommendations: acute COVID-19 – signs and symptoms of COVID-19 for up to 4 weeks, post-COVID-19 syndrome – signs and symptoms that develop during or after an infection, continue for more than 4 weeks and are not explained by an alternative diagnosis. Patients can have various abnormal hematologic parameters during acute COVID-19 infection, such as lymphocytopenia and neutrophilia, thrombocytopenia or thrombocytosis, hyperferritinemia, elevated C-reactive protein, procalcitonin, lactate dehydrogenase, fibrinogen, D-dimer, prolonged prothrombin time, activated partial thromboplastin time. Some of them, such as quantitative platelets changes, can stay or emerge in the postcovid period. Immune thrombocytopenia, also known as immune thrombocytopenic purpura (ITP), has been reported in previous studies. Clinical manifestations of thrombocytopenia are related to the small number of thrombocytes and range from the absence of symptoms to mild/moderate mucocutaneous bleeding (purpura, petechiae, nosebleeds, or bleeding gums) and sometimes to a life-threatening hemorrhage.

Aim. To determine the presence and frequency of changes in the number of platelets after acute COVID-19 infection; to analyze the clinical characteristics, diagnostic work-up, therapeutic strategies, and outcomes of confirmed COVID-19 patients presenting with new-onset ITP.

Materials and methods. We examined 53 patients with a history of confirmed COVID-19, including 30 women and 23 men aged 19 to 82 years. The research was conducted following the Declaration of Helsinki. Written informed consent was obtained from all patients. Determination of platelet count was performed on an automatic hematology analyzer «Sysmex KX-21» (Japan). The studies were performed 2 weeks or more after the first symptoms of COVID-19 followed by follow-up for three months. The results of previous general blood tests performed on other automatic hematology analyzers were also taken into account. Interquartile range (IQR) was counted by the Interquartile range calculator.

Results. Total documents of 47 patients were considered to be eligible for further analysis, which includes 23 patients (48.9 %) who had quantitative platelets changes after the disease. Thrombocytosis was in 27.6 % cases, thrombocytopenia – in 21.3 % cases. Quantitative platelets changes are more common in elderly patients. The median age of patients with thrombocytosis was 62 years, with thrombocytopenia – 64 years. Some patients had signs of cutaneous manifestations in form of petechiae/purpura/ecchymoses or mucosal bleeding (epistaxis, menorrhagia) at the time of diagnosis of ITP. Thrombocytopenia developed between 2 to 6 weeks from the onset of COVID-19 symptoms. Asymptomatic patients with platelet counts of more than $30 \times 10^9/L$ have received no treatment. Symptomatic patients were treated with glucocorticoids, thrombopoietin receptor agonist (TP-RA), or platelet transfusions (all patients respond to this therapy). Secondary Evans syndrome was diagnosed in one case.

Conclusions. Elevation in the platelet count was secondary to inflammation (reactive thrombocytosis). According to the data, ITP can occur not only during active infection but also in the post-recovery period. The most common mechanism suggested for thrombocytopenia has been immune-mediated destruction due to molecular mimicry between platelet surface integrins such as glycoproteins (GPIb/IX, V, GPIIb, or GPIIIa) and virus antigens. A good initial response to a short course of glucocorticoids has been found. TP-RA and platelet transfusions were used as a second-line in few cases.

Keywords: immune thrombocytopenia; COVID-19; postcovid syndrome; thrombocytosis; Evans syndrome.

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КІЛЬКІСНІ ЗМІНИ ТРОМБОЦИТАРНОЇ ЛАНКИ ГЕМОПОЕЗУ В ДИНАМІЦІ ПЕРЕБІГУ COVID-19

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Резюме

Вступ. Коронавірусна хвороба (COVID-19) – це інфекційне захворювання, що викликається коронавірусом тяжкого гострого респіраторного синдрому (SARS-CoV-2) та може перебігати як безсимптомно, так і критично тяжко з множинними ускладненнями. До розвитку тяжкого перебігу захворювання більш схильні люди похилого віку та пацієнти з численними факторами ризику чи супутньою патологією. Згідно з рекомендаціями NICE термін «гострий період COVID-19» використовується для опису ознак та симптомів COVID-19, що розвиваються протягом перших 4-х тижнів, «постковідний період/синдром» –

для опису ознак та симптомів, що розвиваються під час або після захворювання, зберігаються більше 4 тижнів і не мають альтернативного діагнозу. Під час гострого періоду COVID-19 можуть спостерігатися такі гематологічні порушення, як лімфопенія і нейтрофілоз, тромбоцитопенія чи тромбоцитоз, підвищений рівень С-реактивного білка, прокальцитоніну, лактатдегідрогенази, фібриногену, Д-димеру, подовжений протромбіновий час та активований частковий тромбoplastиновий час. Деякі з них, такі як зміни кількості тромбоцитів, можуть зберігатись, або ж виникати у постковідному періоді. Наприклад, у наявних дослідженнях повідомляється про виникнення імунної тромбоцитопенії, відомої як імунна тромбоцитопенічна пурпура (ІТП), клінічні прояви якої варіюють від відсутності симптомів до висипань (пурпура, петехії) чи кровотечі зі слизових оболонок (носова кровотеча, кровоточивість ясен), а іноді – кровотечі, що загрожують життю.

Мета. Визначити наявність та частоту зміни кількості тромбоцитів після гострої інфекції COVID-19; проаналізувати клінічні характеристики, діагностування, терапевтичну стратегію та результати лікування пацієнтів з ІТП, що виникла після COVID-19.

Матеріали і методи. Було обстежено 53 пацієнта з підтвердженням COVID-19 в анамнезі, серед яких було 30 жінок та 23 чоловіків віком від 19 до 82 років. Визначення кількості тромбоцитів проводилося на автоматичному гематологічному аналізаторі «Sysmex KX-21» (Японія). Дослідження проводились через 2 тижні і більше після появи перших симптомів COVID-19 з подальшим контролем протягом трьох місяців. Також враховувалися результати попередніх загальних аналізів крові, виконаних на інших автоматичних гематологічних аналізаторах. Міжквартильний діапазон (ІQR) був підрахований за допомогою калькулятора міжквартильного діапазону.

Результати. Всього документи 47-ми пацієнтів виявились придатними для подальшого аналізу, включаючи 23-х пацієнтів (48,9 %), у яких були виявлені кількісні зміни тромбоцитів після COVID-19. У 27,6 % випадків спостерігався тромбоцитоз, у 21,3 % випадків – тромбоцитопенія. Кількісні зміни тромбоцитів частіше зустрічались у пацієнтів похилого віку. Середній вік пацієнтів з тромбоцитозом становив 62 роки, з тромбоцитопенією – 64 роки. Деякі пацієнти з тромбоцитопенією мали шкірні прояви у вигляді петехій/пурпури/ екхімозів або кровотеч із слизових оболонок (носові кровотечі, менорагія). Тромбоцитопенія виникала протягом 2–6 тижнів від початку симптомів COVID-19. Безсимптомні пацієнти з кількістю тромбоцитів більше $30 \times 10^9/\text{л}$ не отримували лікування. Для лікування пацієнтів, які мали симптоми тромбоцитопенії, були застосовані глюкокортикоїди, агоністи рецепторів тромбопоетину або тромбоконцентрат (усі пацієнти відреагували на цю терапію). В одному випадку був діагностований вторинний синдром Еванса.

Висновки. Тромбоцитоз, що спостерігається під час коронавірусного захворювання, виникає у відповідь на запалення (реактивний/симптоматичний тромбоцитоз). Згідно з отриманими даними, ІТП може виникнути не тільки під час гострого періоду, але і в період після одужання. Найбільш вірогідним механізмом

виникнення тромбоцитопенії є імунно-опосередковане руйнування тромбоцитів через молекулярну мімікрію між поверхневими інтегринами тромбоцитів, такими як глікопротеїни (GPIb/IX, V, GPIIb або GPIIa) та антигенами вірусу. Спостерігалась позитивна динаміка при лікуванні COVID-асоційованої ІТП глюкокортикоїдами. У кількох випадках агоністи рецепторів тромбопоєтину і/або тромбоконцентрат використовувалися як друга лінія терапії.

Ключові слова: імунна тромбоцитопенія, COVID-19, постковідний синдром, тромбоцитоз, синдром Еванса.

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an infectious disease that first emerged in Hubei province, China, in December 2019. The SARS-CoV-2 enters the human body and binds to angiotensin-converting enzyme-2 receptors, which are expressed in most tissues and organs of the body. Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. Patients who are older or have multiple risk factors or comorbidities have an increased risk of developing severe illness. The main symptoms of coronavirus are high temperature, cough, loss or change sense of smell or taste, fatigue, muscle aches, headache, nausea or vomiting, diarrhea. Patients can have various abnormal hematologic parameters during acute COVID-19 infection, such as lymphocytopenia and neutrophilia, thrombocytopenia or thrombocytosis, hyperferritinemia, elevated C-reactive protein, procalcitonin, lactate dehydrogenase, fibrinogen, D-dimer, prolonged prothrombin time, activated partial thromboplastin time. Some of them, such as quantitative platelets changes, can stay or emerge after an acute period (in postcovid period) [1, 2].

Thrombocytosis is defined as an abnormal platelet count, typically $> 450 \times 10^9/L$.

Thrombocytopenia is a medical condition characterized by a low platelet count ($< 100 \times 10^9/L$). Clinical manifestations are related to the small number of thrombocytes and range from the absence of symptoms to mild/moderate mucocutaneous bleeding (purpura, petechiae, nosebleeds, or bleeding gums) and sometimes to a life-threatening hemorrhage. Immune thrombocytopenia, or immune thrombocytopenic purpura (ITP), is the result of our immune system that focuses its attack on self-antigens and destroys platelets. [3] The incidence of ITP in patients after COVID-19 has been variable across studies. [1, 2]

Aim. To determine the presence and frequency of changes in the number of platelets after acute COVID-19 infection; to analyze the clinical characteristics, diagnostic work-up, therapeutic strategies, and outcomes of confirmed COVID-19 patients presenting with new-onset ITP.

Materials and methods

We examined 53 patients with a history of confirmed COVID-19, including 30 women and 23 men aged 19 to 82 years. The research was conducted following the Declaration of Helsinki. Written informed consent was obtained from all patients. Determination of platelet count was performed on an automatic hematology analyzer «Sysmex KX-21» (Japan). The studies were performed 2 weeks or more after the first symptoms of COVID-19 followed by follow-up for three months. The results of previous general blood tests performed on other automatic hematology analyzers were also taken into account. Interquartile range (IQR) was counted by the Interquartile range calculator.

Results

Total documents of 47 patients were considered to be eligible for further analysis, which includes 23 patients (48.9 %) who had quantitative platelets changes after the disease. All patients had a positive SARS-CoV-2 RT-PCR. In all cases, a previous normal platelet count was obtained, or the patient had no previous history of bleeding; alternative diagnoses were considered. Therefore, viral markers for hepatitis B, C, human immunodeficiency virus, and cytomegalovirus were within normal limits. Thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, sepsis, or drug-induced thrombocytopenia were excluded. CBCs of two patients, who had presented with exacerbation of previously diagnosed chronic or persistent ITP, were eliminated from the analysis.

Thrombocytosis was seen in 27.6 % of cases (13 patients). Platelet counts were between $456 \times 10^9/\text{L}$ and $1206 \times 10^9/\text{L}$. The median age of patients was 62 years. 30.8 % (4 patients) were males and 69.2 % (9 patients) were females. The onset of thrombocytosis was from the first day of the disease (and can persist for several weeks to months) to the third month after the acute COVID-19. There was no association with thrombosis or hemorrhage.

Thrombocytopenia was present in 21.3 % of cases (10 patients). Platelets number were between $3 \times 10^9/\text{L}$ and $89 \times 10^9/\text{L}$. Thrombocytopenia developed between 2 to 6 weeks from the onset of COVID-19 symptoms. ITP has been found to be more common in elderly patients. Data of demographic profiles of patients with immune thrombocytopenia secondary to COVID-19 have been presented in Table 1.

In some cases, thrombocytopenia is accompanied by abrupt onset of mucosal bleeding (epistaxis, menorrhagia) or bruising and petechiae.

Asymptomatic patients with platelet counts of more than $30 \times 10^9/\text{L}$ have received no treatment. Symptomatic patients were treated with glucocorticoids, thrombopoietin receptor agonist (TP-RA), or platelet transfusions (all patients respond to this therapy).

**Table 1. Demographic profiles of patients
with immune thrombocytopenia secondary to COVID-19**

Baseline parameters (n = 10)	Value
Age (years) (Median [IQR])	64 [IQR 54.1–76]
Age group	18–49 years (n = 2.20%), ≥ 50 years (n = 8.80%)
Gender	Male (n = 4.40%), Female (n = 6.60%)

First-line treatment consisted of corticosteroids alone (i.e. prednisone 1 mg/kg/day), then TP-RA was added if needed. One patient received platelet transfusions in addition to glucocorticoids and TP-RA. Outcomes to treatment were categorized into two groups: response to treatment and complete response. Response and complete response were defined according to standardized international criteria: platelet count of $> 30 \times 10^9/l$ with at least a doubling of the baseline value, and platelet count of $> 100 \times 10^9/l$ respectively. All patients achieved at least a response during 3 months of follow-up.

Secondary Evans syndrome was diagnosed in one case (immune thrombocytopenia was followed by autoimmune hemolytic anemia, which was confirmed by a direct anti-globulin test). This patient responded to treatment with glucocorticoids and TP-RA.

Data have been presented in Table 2.

**Table 2. Clinical characteristics and outcomes in patients
with immune thrombocytopenia secondary to COVID-19**

Clinical characteristics	Value
Bleeding manifestations (n = 10)	Epistaxis and/or menorrhagia (n = 2.20%), Bruising and petechiae (n = 3.30%), None (n = 5.50%)
Days from onset of COVID-19 symptoms to ITP diagnosis (Median [IQR])	28.3 [IQR 14.5 – 42.2]
Nadir platelet count ($\times 10^9/L$)	3
Management	Glucocorticoids (n = 2.20%), Glucocorticoids + TP-RA (n = 1.10%), TP-RA only (n = 1.10%), Platelet transfusions + glucocorticoids, then - TP-RA (n = 1.10%), Observation only (n = 5, 50%)
Reported outcomes to treatment (n = 5)	Complete response (n = 4, 80%), Response (n = 1.20%)
Evans syndrome secondary to COVID-19	Present (n = 1.10%)

Discussion and conclusions

Elevation in the platelet count was secondary to inflammation (reactive thrombocytosis). Every patient had no thrombosis or hemorrhage and no evidence of chronic myeloproliferative disease.

ITP has been described following several viral infections, including hepatitis B and C viruses, cytomegalovirus, Epstein–Barr virus, varicella zoster virus, human immunodeficiency virus [4]. Multiple cases of ITP secondary to COVID-19 have already been reported before [5, 6, 7]. According to the first comprehensive systematic review of new-onset ITP secondary to COVID-19, comprising 45 cases described in the literature, and our research, we can assume that SARS-CoV-2 can cause ITP and can occur not only during active infection but also in the post-recovery period [2].

Various mechanisms of thrombocytopenia have been suggested, including decreased platelet production and enhanced platelet destruction, as for other viral infections. Most likely that thrombocytopenia can be a result of increased platelet destruction caused by immunologic responses (binding of auto-antibodies to platelets, which leads to enhanced platelet removal from the circulation by reticuloendothelial cells). Whether SARS-CoV-2 can trigger an autoimmune reaction against platelets and red blood cells remains unclear, but the commonest mechanism suggested for thrombocytopenia has been immune-mediated destruction due to molecular mimicry between platelet surface integrins such as glycoproteins (GPIb/IX, V, GPIIb, or GPIIIa) and virus antigens [8]. A systematic approach is essential to diagnose new-onset ITP after excluding several concomitant factors or conditions that can cause thrombocytopenia because immune thrombocytopenia is often a retrospective diagnosis based on the exclusion of other possible causes of thrombocytopenia and assessment of the response to treatment [9].

According to the results of the data, first-line therapy in adults with immune thrombocytopenia with/after COVID-19 is corticosteroid therapy, whose dose and duration should be kept to a minimum. TP-RA or/and platelet transfusions is either a second-line therapy in case of corticosteroid failure or used in order to immediately raise the platelet count and to control or prevent bleeding. Initial response to standard ITP treatments seems very good, with no strong safety signal and especially regarding the risks of thrombosis.

In addition, we report a case of COVID-19 associated immune thrombocytopenia, which causes platelet destruction, and hemolytic anemia, which causes red cell destruction (secondary Evans syndrome). Cases of Evans syndrome have been already mentioned in the articles [10]. Although specific management guidelines are lacking for Evans syndrome, glucocorticoids are

often considered the first-line therapy. Second-line therapies include immunosuppressive agents such as rituximab, mycophenolate mofetil, cyclosporine, and cyclophosphamide [11].

Diagnosing ITP or Evans syndrome secondary to COVID-19 can be a major challenge for clinicians due to various concomitant conditions or factors associated with COVID-19. Here, the causal relationship between SARS-CoV-2 infection and ITP was supported by several points: 1) the time of occurrence (after the second week of infection as reported for other virus-induced ITPs); 2) the exclusion of alternative causes, in particular, no evidence of sepsis-induced thrombocytopenia and disseminated intravascular coagulation; 3) response to steroids; 4) the low rate of recurrence as usually observed in ITP triggered by acute viral infections.

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