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ORIGINAL ARTICLE

THE RELATIONSHIP BETWEEN IMMUNE THROMBOCYTOPENIA WITH THE SEASONS AND COVID-19

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ABSTRACT

Aims: The aim of this study is to observe the correlation between viral infections and seasonal changes and the disease.

Methods: This study was conducted retrospectively with 98 patients diagnosed with immune thrombocytopenia between 2018 and 2022. Data regarding patients' demographic information, laboratory results, presence of coronavirus disease 2019 infection, seasonal and monthly distribution of infection, coronavirus disease 2019 vaccination history, and presence of active treatment were collected. The relationship between immune thrombocytopenia and viral infections according to seasons, the change in the number of patients diagnosed with immune thrombocytopenia before and after March 2020 due to the restrictions during the pandemic period, and the difference in platelet counts in patients who were vaccinated against coronavirus disease 2019 were investigated.

Results: In immune thrombocytopenia cases, which are possibly triggered by viral infections, when we investigated whether there was a seasonal difference, it was seen that the number of patients diagnosed with immune thrombocytopenia was higher in spring and summer. However, when statistical analysis was performed, no significant difference was found in terms of new diagnoses between seasons. On the other hand, a statistically significant difference was found between months. When examined on a monthly basis, it is seen that patients were diagnosed more frequently in June and October.

Conclusion: It was determined that the months of diagnosis were close to each other in our study, and the literature showed us that we need to consider the characteristics of these months in etiology.

Keywords: Coronavirus disease 2019, hematology, immune thrombocytopenia

INTRODUCTION

The hematological condition known as immune thrombocytopenia is typified by autoantibodies targeting platelets in the reticuloendothelial system and destroying them (1). Immune thrombocytopenia in children is typically acute, self-limiting, and tends to appear in winter and fall, possibly triggered by viral infections or vaccinations. Many affected children report flu-like symptoms in the weeks before developing immune thrombocytopenia. On the other hand, immune thrombocytopenia in adults is generally chronic, and the seasonal variability of this disease is unknown (2).

Autoantibodies against platelet surface glycoproteins contribute significantly to both the impaired production and destruction of platelets in immune thrombocytopenia. Cytotoxic T lymphocytes also play a role in the pathophysiology of immune thrombocytopenia, involving interactions between B and T lymphocytes and inflammatory cytokines. In primary immune thrombocytopenia, autoantibodies against antigens

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like Glycoprotein IIb/IIIa (GP IIb/IIIa) and GPIb/IX lead to reduced platelet production and increased destruction. Studies have identified autoreactive T cell clones against GPIIb/IIIa in immune thrombocytopenia patients, alongside cytotoxic T cells targeting autologous platelets. Additional evidence includes an imbalanced T helper cell type 1(Th1)/Th2 ratio, increased Th17 cells, elevated interleukin-17 levels, and reduced regulatory T cells (2).

Immune thrombocytopenia can be a primary condition or occur secondary to other disorders. Secondary causes include viral infections such as Epstein-Barr virus, cytomegalovirus, and hepatitis C; certain medications; and autoimmune diseases such as antiphospholipid antibody syndrome (2, 3).

Primary immune thrombocytopenia is an acquired immune disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count of less than $100x10^9$/L. This condition is caused by the presence of pathogenic anti-platelet autoantibodies, T cell-mediated destruction of platelets, and impaired function of megakaryocytes. In adults, primary immune thrombocytopenia typically progresses to a chronic state, making it necessary to seek treatment aimed at restoring a durable platelet count to ensure adequate hemostasis (4).

In adults, primary immune thrombocytopenia affects about 80% of patients, with secondary immune thrombocytopenia affecting the remaining 20%. Primary immune thrombocytopenia can affect up to 9.5 out of every 100,000 individuals, and as people age, its incidence rises to about 3.3 out of every 100,000 adults annually. Immune thrombocytopenia is more common in women, but in children and the elderly, it is observed more frequently in men (5).

Petechiae, purpura, and mucosal bleeding in the mouth, gastrointestinal tract, and urinary tract, including nosebleeds, are possible symptoms. Additionally, a lower quality of life may be experienced. In approximately 0.2% of cases, cerebral hemorrhages can be fatal in the worst circumstances (4).

Depending on the disease duration, immune thrombocytopenia is classified into newly diagnosed, persistent, and chronic. Immune thrombocytopenia that is newly diagnosed is classified as occurring within three months of diagnosis, persistent immune thrombocytopenia occurs between three and twelve months after diagnosis, and chronic immune thrombocytopenia lasts more than twelve months (2).

Treatment strategies for immune thrombocytopenia aim to restore platelet counts to levels that support adequate hemostasis rather than striving for normal physiological platelet counts. First-line treatments primarily focus on inhibiting the production of autoantibodies and reducing platelet degradation. Second-line treatments include immunosuppressive medications, such as rituximab, and may involve splenectomy. Finally, third-line treatments seek to stimulate platelet production by megakaryocytes (4).

The mechanism of immune thrombocytopenia remains incompletely known, but it is believed to be linked to viral infections. Data about its association with the coronavirus disease 2019 (COVID-19) is scarce (6). Furthermore, numerous studies indicate that it is associated with seasonal variations and fluctuates by month (2). Due to the paucity of available research on the effects of these two conditions on the disease, we conducted a retrospective study including patients diagnosed with immune thrombocytopenia at the Hematology Department of Trakya University School of Medicine between 2018 and 2022.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (approval number: 08/31, dated: 08.05.2023).

Data for this study were collected through the Trakya University School of Medicine Database between January 2018 and December 2022. This study was conducted retrospectively with 98 patients, 64 women and 34 men, who were diagnosed with immune thrombocytopenia at Trakya University Hematology Clinic between 2018 and 2022.

Patients

In our study, the diagnosis of immune thrombocytopenia was made based on the criteria: "Thrombocytopenia (<100,000/μL), absence of anemia (excluding anemia due to bleeding and/or iron deficiency), normal leukocyte count (though mild abnormalities in leukocyte count may be observed), and no morphological evidence of dysplasia in any blood cell type in the blood smear". A total of 98 patients who met these criteria were included. No specific gender distinction was made, and individuals of all genders and ages who were diagnosed with immune thrombocytopenia at our clinic during the specified years were included in the study. Patients with additional diseases other than immune thrombocytopenia were not included in the study. These patients presented to our clinic between 2018 and 2022, either with complaints of bleeding or other symptoms, and received this diagnosis. Additionally, patients who were referred to our clinic from other departments of our hospital due to low platelet counts and were diagnosed with immune thrombocytopenia were also included. Hemoglobin, platelet count, activated partial thromboplastin time, and prothrombin time values were recorded for the patients.

Collected Data

The diagnosis of COVID-19 was based on positive polymerase chain reaction test results. Patients who had already been diagnosed with immune thrombocytopenia were categorized as "positive", "negative", or "unknown" based on their COVID-19 infection status during the study.

The vaccination status of 55 patients in the study was obtained. The vaccines administered were Sinovac and BioNTech. However, since the study did not focus on the distribution of these vaccines by manufacturer, the only parameter examined was whether the patients were vaccinated with one of these two vaccines.

Platelet values before vaccination were available for 45 patients, and platelet values after vaccination were available for 37 patients. The study aimed to determine whether there was a significant difference in platelet counts following vaccination.

The study also focused on the seasons and months in which the patients were diagnosed. The data were analyzed to investigate whether there was a correlation between the diagnosis of immune thrombocytopenia and the seasons or the months of the year.

The presence or absence of active treatment was recorded for 94 patients. Data on the patients' demographic information, laboratory results, presence of COVID-19 infection, the infection's seasonal and monthly distribution, COVID-19 vaccination history, and presence of active treatment were collected.

The relationship between immune thrombocytopenia and viral infections by the seasons, the change in the number of immune thrombocytopenia diagnoses before and after March 2020 due to the restrictions during the pandemic, and the difference in platelet counts in patients who were vaccinated for COVID-19 were investigated.

Statistical Analysis

The data were analyzed with IBM SPSS version 23.0. The comparison of categorical data groups was performed using Fisher's exact test to detect new diagnoses according to seasons and the chi-squared test as appropriate. The Kruskal-Wallis test was used to evaluate the significance of differences between patient groups that were aware of the diagnostic platelet value of patients diagnosed in different seasons. The Wilcoxon test was used to compare the values of patient groups whose platelet values were measured before and after vaccination. The chi-squared test was used to evaluate the difference between gender groups diagnosed in different seasons. For all analyses, a p-value threshold of <0.05 was accepted as statistically significant.

RESULTS

The number of newly diagnosed patients each year was as follows: 2018: 21 (21.4%), 2019: 25 (25.5%), 2020: 25 (25.5%), 2021: 20 (20.4%), and 2022: 7 (7%). Of the newly diagnosed cases, 63 were female and 35 were male (Table 1).

When the platelet values of the patients before the COVID-19 vaccination were examined, it was seen that this data was available in 45 patients, the mean value was 126,177 [standard deviation (SD) 104,147], and the median was 86,000. When the post-vaccination data of the 37 patients were examined, it was determined that the mean platelet count was 91,837 (SD 87,174) and the median was 61,000. No significant difference was found in platelet count before and after the COVID-19 vaccine (p=0.053) (Table 2).

When we investigated whether there was a seasonal difference, no difference was found in terms of new diagnoses according to the seasons (p=0.059). However, significant differences were found on a monthly basis (p<0.001).

In our study, 98 patients with immune thrombocytopenia were diagnosed more frequently in summer (30.3%) (30 patients) and spring (27.3%) (27 patients). However, there was no statistically significant difference in the number of newly diagnosed cases between seasons (Figure 1).

When we examined the times of new diagnoses on a monthly basis, it was found that diagnoses were made more frequently in June (14.28%) (14 patients) and October (13.26%) (13 patients). On the other hand, we found September (4.08%) (4 patients) and November (4.08%) (4 patients) to be the months with the least number of diagnoses. A statistically significant difference was found in diagnosis according to months (Figure 2).

During the same period, 19.4% of patients (19 patients) were diagnosed with COVID-19, 39.8% (39 patients) were undiagnosed, and the COVID-19 status of 40.8% (40 patients) was unknown (Figure 3).

Out of 98 patients, 25.8% (25 patients) were actively receiving treatment, while 74.2% (73 patients) were not (Figure 4).

Table 1: Number of patients diagnosed with immune thrombocytopenia.

	Female	Male
Number of patients (min.-max.)	63 (18-80)	35 (18-93)
Average age + SD	45.05+16.068	48.65+22.49

SD: Standard deviation, min.-max.: Minimum-maximum

Table 2: Pre and post vaccination values of platelet.

	Pre-vaccination	Post-vaccination
Median (min.-max.)	86000 (4000-438000)	61000 (4000-299000)
Avarage age + SD	126177+104147	91837+87174

SD: Standard deviation, min.-max.: Minimum-maximum

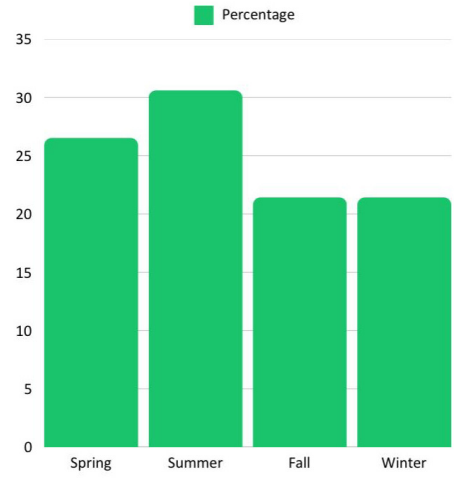

Figure 1: Seasonal distribution of patients diagnosed with immune thrombocytopenia.

COVID-19 vaccination information is available for only 55 patients. 96.4% (53 patients) of whom were vaccinated and 3.6% (2 patients) were not vaccinated (Figure 5).

DISCUSSION

The exact mechanism of immune thrombocytopenia is not fully understood. Numerous studies have proposed that the disease is initiated by a viral infection, with pre-formed antibodies cross-reacting with platelet surface integrins such as glycoprotein Ib-IX-V or glycoprotein IIb/IIIa6,7. While immune thrombocytopenia has been linked to numerous viral infections, there is limited information about its connection to COVID-19 (6).

In the study of Bhattacharjee and Banerjee (7), examining 45 cases of new-onset immune thrombocytopenia due to COVID-19, it is stated that immune thrombocytopenia may occur secondary to COVID-19 infections. In another case report, evidence from the treatments' effectiveness and the absence of other underlying factors indicated that COVID-19 was the cause of immune thrombocytopenia in this instance (8). In our study, we found the number of newly diagnosed patients higher in 2019 and 2020. However, it should be discussed whether this supports our conclusion.

The relationship between immune thrombocytopenia and viral infections is known, so we wanted to investigate whether there was a seasonal difference (6). In a multicenter study conducted by Tombak et al. (2) in Türkiye, the rate of patients diagnosed with immune thrombocytopenia, especially in the spring, was much higher than in other months. Some studies in the literature also support the fact that immune thrombocytopenia diagnosis differs significantly according to months (2). We did not find a significant seasonal difference in our study, but when we looked at the rate of patients diagnosed according to months, we found a significant difference between months in our hospital. We found that the rate of patients diagnosed in June and October was higher than in other months.

Immune thrombocytopenia is a diagnosis of exclusion in the evaluation of thrombocytopenia. Although its pathogenesis is not completely clear, the leading theory suggests that viral antigens cross-react with normal platelet antigens in a molecular mimicry manner, triggering the destruction of platelets (8). It is conceivable that a comparable mechanism exists with COVID-19 or that COVID-19 could lead to a worsening of a

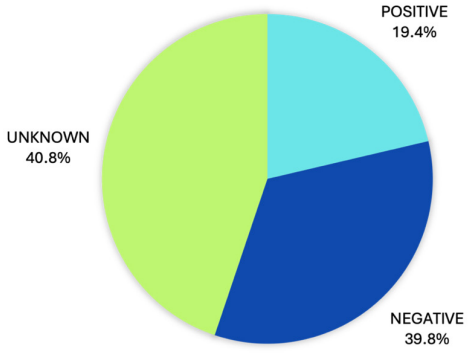

Figure 2: Percentage distribution of patients on a monthly basis.

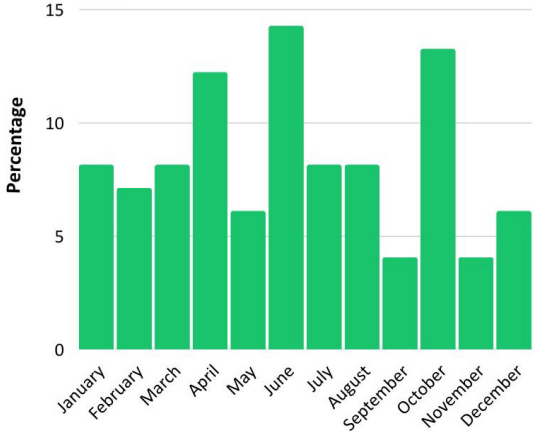

Figure 3: COVID-19 diagnosis rates of patients.
COVID-19: Coronavirus disease 2019

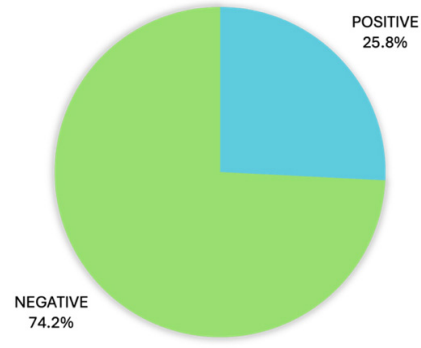

Figure 4: Treatment situations of patients diagnosed with immune thrombocytopenia.

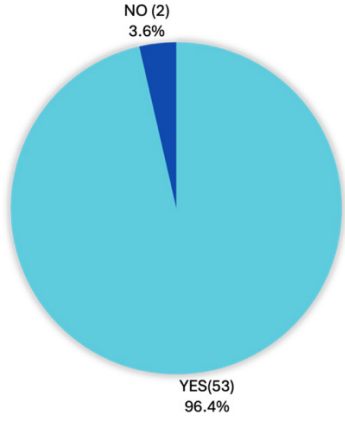

Figure 5: COVID-19 vaccination status of patients.
COVID-19: Coronavirus disease 2019

pre-existing low-grade immune thrombocytopenia disorder (8). Since we could not fully access the data on patients' COVID-19 infection in our study, our results on this subject are open to improvement.

In one study, thrombocytopenia flare-ups occurred in 12% of chronic immune thrombocytopenia patients after COVID-19 vaccination. Thrombocytopenia flare-ups usually occurred 2-5 days after vaccination, but despite this, recommendations for the first dose of the COVID-19 vaccine continued (9). In our study, no significant relationship was found between the COVID-19 vaccine and pre- and post-vaccination platelet values. The mean platelet values of patients before vaccination were found to be higher than the platelet values after vaccination.

In our study, we did not find gender differences in the occurrence of immune thrombocytopenia according to the seasons. The fact that Tombak et al. (2) reached the same conclusion in their study supports our result.

Study Limitations

Our study was limited in evaluating some dates due to limitations in accessing patient data. However, the fact that the months of diagnosis in our study were consistent with the literature was a supportive study for the limited studies conducted on this subject. However, more comprehensive studies using larger patient groups are needed on this subject.

CONCLUSION

In our study, the number of patients diagnosed with immune thrombocytopenia was significantly higher in June and October. This result, which is consistent with the literature, shows that changes in etiology depending on the months should be taken into consideration.

Various studies demonstrate the relationship between COVID-19 and immune thrombocytopenia and suggest that it may have a negative effect on the prognosis of the disease. In our retrospective study, 19 of the patients with immune thrombocytopenia had COVID-19 infection. Fifty-three patients whose data we could access had COVID-19 vaccines. There was no significant difference in the platelet values of patients who received the COVID-19 vaccine before and after vaccination. However, more detailed studies are needed on the long-term effects of COVID-19 and its vaccine on a larger number of patients diagnosed with immune thrombocytopenia.

As revealed in our study, immune thrombocytopenia has been observed to be more prominent, especially in the months of seasonal transition and during epidemic periods when viral infections are frequently seen, and it should be kept in mind in patients presenting with isolated thrombocytopenia.

Ethics

Ethics Committee Approval: *This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (approval number: 08/31, dated: 08.05.2023).*

Informed Consent: *Retrospective study.*

Footnotes

Conflict of Interest: *The authors declared no conflict of interest.*

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