



Original Article

Hematological Abnormalities Beyond Lymphocytosis During Infectious Mononucleosis: Epstein-Barr Virus-Induced Thrombocytopenia

Emilio-Manuel Páez-Guillán, Joaquín Campos-Franco, Rosario Alende and Arturo Gonzalez-Quintela.

Department of Internal Medicine, Complejo Hospitalario Universitario, University of Santiago de Compostela, Spain.

Competing interests: The authors declare no conflict of interest.

Abstract. Background: Thrombocytopenia during Epstein-Barr virus mononucleosis is well-known; however, no recent series have investigated its frequency, associated factors, and evolution. The present study aimed to investigate platelet count characteristics in adult patients with infectious mononucleosis.

Methods: We reviewed the clinical records of 400 patients admitted to the hospital with infectious mononucleosis (52.0% male; median age, 19 years [range, 15-87 years]), focusing on blood platelet counts, thrombocytopenia prevalence and outcomes.

Results: Thrombocytopenia (platelet count $\leq 150 \times 10^9/L$) was present in 119 (29.7%) patients. Thirty-two (8.0%) patients showed platelet counts lower than $100 \times 10^9/L$. Thrombocytopenia was severe (platelets $< 50 \times 10^9/L$) in 6 (1.5%) patients. Thrombocytopenia was associated with a lower frequency of typical mononucleosis symptoms such as sore throat and lymphadenopathy, lower frequency of positive heterophil antibodies, higher serum bilirubin concentration and prothrombin time, lower blood leukocyte and lymphocyte count, lower concentration of serum immunoglobulin G and immunoglobulin A concentrations, and larger spleen size. Thrombocytopenia normalized quickly during follow-up. Only 2 cases required specific therapy. Platelet counts significantly increased during follow-up, even in cases without baseline thrombocytopenia. There were no significant hemorrhagic complications.

Conclusions: Transient thrombocytopenia is common during infectious mononucleosis in adult patients. Patients with thrombocytopenia have distinct clinical and biological features; it is typically mild during infectious mononucleosis. Cases of severe thrombocytopenia are rare and were not associated with hemorrhagic complications in this series.

Keywords: Epstein-Barr virus; Infectious mononucleosis; Platelets; Thrombocytopenia.

Citation: Páez-Guillán E.M., Campos-Franco J., Alende R., Gonzalez-Quintela A. Hematological abnormalities beyond lymphocytosis during infectious mononucleosis: epstein-barr virus-induced thrombocytopenia. *Mediterr J Hematol Infect Dis* 2023, 15(1): e2023023, DOI: <http://dx.doi.org/10.4084/MJHID.2023.023>

Published: March 1, 2023

Received: January 24, 2023

Accepted: February 27, 2023

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Dr. Arturo González Quintela. Department of Internal Medicine, Hospital Clínico Universitario, 15706 University of Santiago de Compostela, Spain. Tel: +34 981 951265, Fax: +34 981 950501. E-mail: arturo.gonzalez.quintela@usc.es

Introduction. Thrombocytopenia, often multifactorial, is common in many viral infections.^{1,2} An alteration in white blood cells is the most prominent feature in primary Epstein-Barr virus (EBV) infection, giving the disease its name (infectious mononucleosis). Additional hematological disturbances, like thrombocytopenia,

sometimes severe, have been less studied, although it is almost always mentioned in descriptions of the disease.³⁻⁶ To date, isolated cases of severe thrombocytopenia continue to be published,⁷⁻¹⁰ but its exact frequency is not well known. A review spanning 30 years found 36 cases of severe (platelets $<20 \times 10^9/L$) thrombocytopenia during EBV-induced infectious mononucleosis.⁷ Classic studies on thrombocytopenia in EBV infection date back to the 1950s and 1960s. In 1956, Pader and Grossman reported 2 cases of severe thrombocytopenia and purpura among 300 consecutive cases of infectious mononucleosis.¹¹ In 1965, Carter observed some degree of thrombocytopenia in 50% of 57 cases;¹² in 1966, Cantow and Kostinas reported thrombocytopenia in 24% of 41 mononucleosis cases.¹³ These classic series continue to be the main reference in the most recent case reports and small series of thrombocytopenia during EBV-induced infectious mononucleosis.^{7-10, 14-17} Since these old series were published, much has changed in the diagnosis of EBV infection and even in the ease of measuring the blood platelet count. The present study evaluated the current prevalence of thrombocytopenia, its severity, associated factors, and evolution in a larger series of adult patients with EBV-induced infectious mononucleosis.

Methods.

Design and setting. We reviewed the clinical records of adult patients (aged 15 years and older) with infectious mononucleosis who were admitted to the University Hospital of Santiago de Compostela (Spain) between 1995 and 2018, as reported elsewhere.^{18,19} The hospital is the reference center for an area including approximately 400,000 inhabitants. The main reasons for hospital admission were severe signs of a systemic inflammatory response, difficulty with oral intake, and complications.

Diagnosis of infectious mononucleosis. A definitive diagnosis of infectious mononucleosis was considered when a compatible clinical syndrome was accompanied by positive immunoglobulin (Ig)M antibodies against the viral capsid antigen of EBV and/or a positive heterophile antibody result, as revealed by either a classic Paul-Bunnell test or a rapid commercial test.⁶ A total of 319 patients (of the 338 tested) had positive immunoglobulin IgM antibodies against the viral capsid antigen, 338 (of the 380 tested) had a positive heterophile antibody result, and 257 patients had both tests positive.

Study population and determinations. A total of 401 patients met the diagnostic criteria. The platelet count was unavailable for 1 case. The study, therefore, included 400 patients (52.0% male; median age, 19 years [range, 15-87 years]). We reviewed their clinical records,

focusing on automated blood cell counts (particularly platelet counts). Platelet counts $>150 \times 10^9/L$ (and $<450 \times 10^9/L$) were considered normal in the present study. Significant thrombocytopenia was considered when the platelet count was below $100 \times 10^9/L$, and severe thrombocytopenia was considered when the platelet count was below $50 \times 10^9/L$. Abnormally low platelet counts were routinely confirmed by blood smear examination. Clinical characteristics, markers of liver damage (serum alanine aminotransferase and bilirubin), prothrombin time, and serum concentrations of immunoglobulins (IgG, IgA, and IgM) were also registered. The first available laboratory determination, usually taken on admission, was used for analyses. Spleen size was measured by routine ultrasound when available. Follow-up of blood counts during convalescence was available for 293 patients (median follow-up, 28 days; interquartile range [IQR] 20-42 days; [range 14-177 days]).

Statistical analyses. We employed the Mann-Whitney test to compare the numerical data between groups and the Wilcoxon test to compare paired samples of numerical values. We employed the chi-squared test (with continuity correction and trend analysis, when appropriate) to compare proportions and the Jonckheere-Terpstra test for trend analysis of numerical variables among ordinal categories. Lastly, we used Spearman's rank test to assess the correlations. All tests were two-tailed.

Ethical approval. The study was reviewed and approved by the institutional Ethics Committee (code 2017/578). The requirement for informed consent from the study participants was waived, in agreement with Spanish regulations for similar retrospective studies.

Results.

Thrombocytopenia prevalence. **Figure 1** is a histogram of the blood platelet counts for the patients with infectious mononucleosis. The median platelet count on admission was $185 \times 10^9/L$ (range 15-441 $\times 10^9/L$; IQR 142-233 $\times 10^9/L$). **Table 1** shows a comparison of the demographic, clinical, and biological characteristics of the patients with normal ($>150 \times 10^9/L$) platelet counts, those with platelet counts of 100-150 $\times 10^9/L$ ($n=87$, 21.7%), and those with platelet counts $<100 \times 10^9/L$ ($n=32$, 8.0%). Six (1.5%) patients had platelet counts $<50 \times 10^9/L$.

Clinical associations. Sex and age were not significantly associated with thrombocytopenia (**Table 1**). Typical symptoms of infectious mononucleosis, such as sore throat and lymphadenopathy, were less common in patients with low platelet counts (**Table 1**). However, spleen size tended to be larger in patients with low

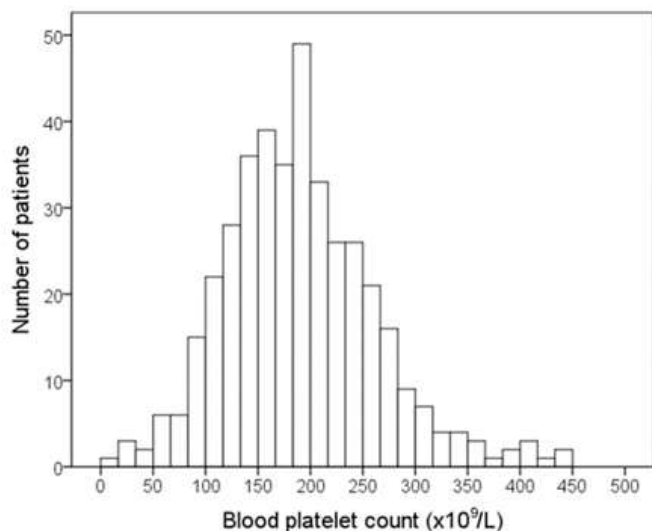


Figure 1. Histogram of platelet counts in patients with infectious mononucleosis (n=400).

platelet counts (**Table 1**). A total of 26 patients received corticosteroid therapy prior to admission. The prevalence of low platelet counts tended to be lower among those patients who received corticosteroids (typically indicated

by the general practitioner due to severe oropharyngeal symptoms that made swallowing difficult) before admission (**Table 1**).

Hematologic associations. Total blood leukocyte counts and differential lymphocyte counts were lower in patients with low platelet counts (**Table 1**). The hemoglobin level was similar in the various platelet count strata (**Table 1**). There were also no significant differences in hemoglobin levels among platelet count categories when patients were stratified by sex (data not shown). The prevalence of anemia was similar among platelet count categories (**Table 1**). No cases of autoimmune hemolytic anemia were detected, although mild anemia was present in a sizeable proportion of cases (**Table 1**). The prothrombin time tended to be longer the lower the platelet count (**Table 1**).

Immunologic associations. Serum IgG and serum IgA concentrations were lower in the patients with low platelet counts (**Table 1**). Serum IgM concentrations were similar in the various platelet strata (**Table 1**). The

Table 1. Demographic, clinical, and biological characteristics of patients with infectious mononucleosis, stratified by baseline blood platelet count during hospital admission.

	Blood platelet count						P-value
	>150 x10 ⁹ /L		100-150 x10 ⁹ /L		<100 x10 ⁹ /L		
	No.		No.		No.		
Age (years)	281	19 (17-23)	87	18 (17-23)	32	18 (17-29)	0.943
Sex (male)	281	144 (51.2)	87	49 (56.3)	32	15 (46.9)	0.939
Sore throat	279	221 (79.2)	87	54 (62.1)	32	13 (40.6)	<0.001
Lymphadenopathy	279	219 (78.5)	87	57 (65.5)	32	21 (65.6)	0.012
Spleen diameter (mm)	140	145 (130-160)	37	155 (140-167)	19	167 (143-171)	<0.001
Splenomegaly (>14 cm)	140	77 (55.0)	37	27 (73.0)	19	16 (84.2)	0.003
Previous corticosteroid therapy	278	22 (7.9)	86	4 (4.7)	32	0 (0.0)	0.060
Hospital stay (days)	281	5 (4-7)	87	6 (4-8)	32	9 (7-12)	<0.001
Death during admission	281	0 (0.0)	87	2 (2.3)	32	1 (3.1)	0.008
Positive heterophile antibody test	270	248 (91.9)	81	69 (85.2)	29	21 (72.4)	<0.001
Serum bilirubin (mg/dL)	272	0.7 (0.4-1.3)	84	1.2 (0.8-2.7)	32	1.2 (0.6-1.8)	<0.001
Prothrombin time (INR)	184	1.06 (1.01-1.14)	58	1.12 (1.06-1.20)	19	1.12 (1.05-1.23)	<0.001
Serum ALT (times the ULN)	279	6.7 (3.2-10.5)	87	7.3 (2.9-11.6)	32	4.7 (1.9-11.1)	0.335
Blood hemoglobin (g/dL)	281	13.5 (12.3-14.5)	87	13.7 (12.6-14.8)	32	13.4 (12.7-15.1)	0.115
Anemia*	281	66 (23.5)	87	20 (23.0)	32	7 (21.9)	0.835
Blood leukocytes (x10 ⁹ /L)	281	12.9 (8.8-17.1)	87	10.2 (5.8-14.4)	32	6.3 (3.1-11.4)	<0.001
Blood lymphocytes (%)	281	53 (44-61)	87	53 (39-62)	32	37 (21-56)	0.011
Serum IgG (mg/dL)	177	1390 (1150-1630)	53	1200 (1030-1370)	27	1130 (1025-1600)	<0.001
Serum IgA (mg/dL)	177	295 (207-378)	53	256 (170-330)	27	211 (171-361)	0.015
Serum IgM (mg/dL)	177	240 (183-338)	53	243 (158-332)	27	188 (145-260)	0.086

Figures are medians and interquartile ranges (within parentheses) or absolute numbers and percentages (within parentheses). No., number of patients with available determination. P-values were obtained with a trend test (chi-square test for categorical variables and Jonckheere-Terpstra test for numerical variables). INR, International Normalized Ratio; ALT, alanine aminotransferase; ULN, upper limit of normal. *Blood hemoglobin <12 g/dL (females) or <13 g/dL (males).

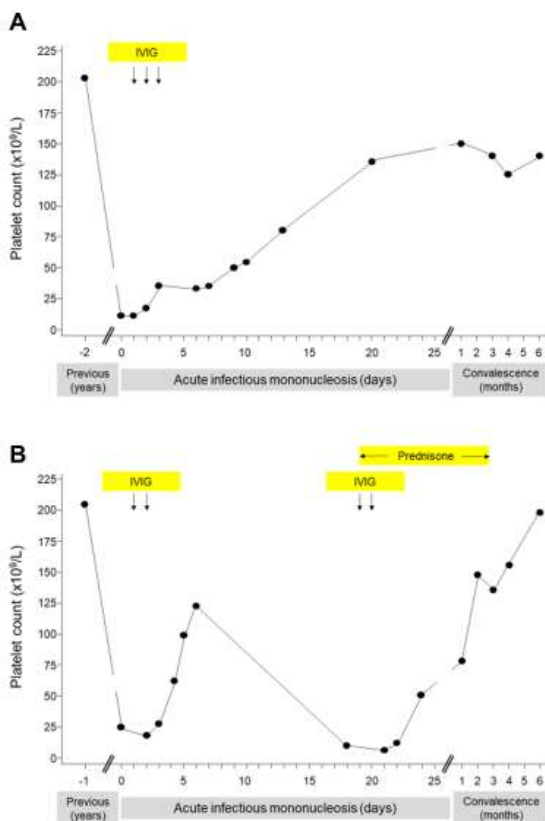


Figure 2. Time-course changes of blood platelet counts in the 2 patients from the series with infectious mononucleosis and platelet counts lower than $20 \times 10^9/L$. The **upper panel (A)** corresponds to a 16-year-old female presenting with fever and sore throat. The lowest platelet count was $14 \times 10^9/L$. On admission, blood hemoglobin was 12.6 g/dL. White blood cell count was $14.0 \times 10^9/L$ (17% neutrophils, 3% monocytes, 3% basophils, 69% lymphocytes, and 8% large unstained cells [LUCs] in the automatic cytometry). Activated lymphocytes were observed in the peripheral blood smear. Both heterophil antibodies (rapid test) and IgM to EBV-viral capsid antigen (VCA) were positive. She was treated with intravenous immunoglobulins (IVIg, 0.6 g/kg) for three consecutive days, with rapid and stable recovery. She did not develop hemorrhagic manifestations. The **lower panel (B)** corresponds to a 17-year-old male presenting with fever, sore throat, and peripheral lymphadenopathy. The lowest platelet count was $9 \times 10^9/L$. On admission, blood hemoglobin was 14.2 g/dL. White blood cell count was $10.1 \times 10^9/L$ (35% neutrophils, 7% monocytes, 2% basophils, 51% lymphocytes, and 5% LUC in the automatic cytometry). Activated lymphocytes were observed in the peripheral blood smear. Both heterophil antibodies (rapid test) and IgM to EBV-VCA were positive. He was initially treated with IVIG (1 g/kg) for 2 consecutive days, with rapid initial recovery. However, severe thrombocytopenia relapsed in the third week. He was treated again with IVIG and corticosteroids (prednisone, initial dose 1 mg/kg). Platelet counts quickly returned to normal. He did not develop hemorrhagic manifestations. Prednisone was maintained for 10 weeks in tapering doses. Platelet counts remained within normal limits during the following months (panel B) and during the following 10 years without specific therapy (data not shown).

prevalence of a positive heterophile antibody test tended to be lower as the level of platelet counts decreased (**Table 1**).

Outcome. No bleeding complications related to thrombocytopenia were recorded. Of the six patients with severe thrombocytopenia (platelets $<50 \times 10^9/L$), there were two patients with counts lower than $20 \times 10^9/L$; both were treated with intravenous immunoglobulins (IVIg), with rapid initial recovery (**Figure 2**). Thrombocytopenia relapsed in one of these two patients after a few weeks, requiring a new course of IVIG and corticosteroid treatment for several weeks, after which the patient maintained normal platelet counts in the following years (**Table 1**). Of the remaining four patients with platelet counts between $20 \times 10^9/L$ and $50 \times 10^9/L$, one died from developing a lymphoproliferative disorder associated with the EBV infection. The other 3 recovered normal platelet counts in less than a month without needing treatment.

Platelet counts tended to increase in all baseline platelet strata, even in those patients with normal platelet counts on admission. However, the increased proportion was greater in the patients with lower platelet levels at baseline (**Table 2**). The vast majority of patients (87 of 88, 98.8%) with platelet counts $\leq 150 \times 10^9/L$ on admission and available follow-up data increased their platelet counts in the immediate convalescent period (**Table 2**).

Among the patients with available follow-up data, 96 received corticosteroids during hospital admission (for reasons different from thrombocytopenia), and 194 did not (data unavailable for 3 cases). The calculated rate of platelet increase per day was not significantly different between patients who received corticosteroids and those who did not (median increase $1.4 \times 10^9/L$ per day [IQR 0.26-3.2 $\times 10^9/L$ per day] versus median increase $2.0 \times 10^9/L$ per day [IQR 0.12-4.4 $\times 10^9/L$ per day], respectively; $P=0.171$).

The three patients who died during hospitalization had low platelet counts (**Table 1**). A 47-year-old male presenting with fever, lymphadenopathy, skin rash, severe anemia, thrombocytopenia, and elevated markers of liver damage died after multiorgan failure due to hemophagocytic syndrome during EBV-related infectious mononucleosis on the 10th day of hospital admission in the intensive care unit. In situ hybridization revealed EBV-DNA in lymph nodes and bone marrow obtained during the autopsy. No specific treatment was established for the hematological process. A 33-year-old female presenting with fever, hepatosplenomegaly, inguinal lymphadenopathy, pancytopenia, jaundice, and elevated markers of liver damage was simultaneously diagnosed with acute EBV infection and natural killer/T-cell lymphoproliferative disorder. Epstein-Barr virus-DNA and EBV-encoded small RNA (EBER) were demonstrated in lymph node biopsy. She died after multiorgan failure due to *Streptococcus mitis* and *Candida albicans*-related sepsis on the 30th day of

Table 2. Time-course changes of blood platelet count in patients with infectious mononucleosis, stratified by their baseline count.

Baseline platelet count category	No.	Baseline platelet count (x10 ⁹ /L) (median and IQR)	Follow-up (days) (median and IQR)	Convalescence platelet count (x10 ⁹ /L) (median and IQR)	Percentage of change (median and IQR)	Cases with platelet increase (n, %)	P-value
>150 (x10 ⁹ /L)	205	207 (182-250)	27 (20-42)	254 (217-299)	18.0 (-3.36-42.7)	142 (69.2)	<0.001
100-150 (x10 ⁹ /L)	66	131 (116-142)	29 (21-42)	227 (185-275)	76.4 (41.7-125.1)	66 (100)	<0.001
<100 (x10 ⁹ /L)	22	75 (65-96)	29 (23-38)	155 (126-207)	97.3 (62.5-176.7)	21 (95.4)	<0.001

No., number of patients with available follow-up. P-values were obtained with the Wilcoxon test for paired samples.

hospital admission in the intensive care unit. Specific treatment for the lymphoma could not be started. A 17-year-old male patient with diabetes mellitus and a severe previous disability died after multiorgan failure due to methicillin-resistant *Staphylococcus aureus* sepsis on the 40th day of hospital admission. As a whole, the hospital stays tended to be longer the lower the platelet count on admission (**Table 1**).

Discussion. Some degree of thrombocytopenia (platelet counts lower than 150 x10⁹/L) was present in nearly a third of patients with infectious mononucleosis admitted to the hospital, confirming classic reports establishing this frequency at between 25% and 50% in smaller series.^{12,13} Moreover, median platelet counts in patients with infectious mononucleosis were very similar to that observed in a series of 47 college outpatients.¹⁴ Severe thrombocytopenia (platelet counts lower than 50 x10⁹/L) was only observed in 1.5% of patients with EBV-induced infectious mononucleosis admitted to the hospital, confirming classic reports.¹¹ More importantly, even patients with normal platelet counts on admission showed an increase in platelet counts during convalescence, thus suggesting that relative thrombocytopenia is a common phenomenon during infectious mononucleosis. It should be noted, however, that the patients in this series were admitted to the hospital, thus selecting the most severe cases.

Moreover, serum bilirubin, prothrombin time, and hospital stay were higher in patients with lower platelet counts, suggesting that thrombocytopenia might be associated with greater disease severity. Along these lines, thrombocytopenia was present in the three patients who died in this series, 2 of whom had EBV-related lymphoproliferative disorders. Finally, it should be noted that all the patients were older than 15 years. It is known that primary EBV infection can be more severe in adulthood than in childhood,³⁻⁶ although no association between age and thrombocytopenia was observed in the present series.

Low platelet counts were associated with some atypical features of infectious mononucleosis, including a lower frequency of sore throat and lymphadenopathy, lower blood leukocyte and lymphocyte counts, lower serum IgG and IgA concentration, and lower frequency of positive heterophil antibodies. These findings suggest

that patients with EBV-induced thrombocytopenia show a distinct clinical syndrome.

Thrombocytopenia normalized quickly during follow-up of infectious mononucleosis without specific therapy in most cases. Even patients with severe thrombocytopenia (platelet counts lower than 50 x10⁹/L) recovered spontaneously, as described in the literature.²⁰ Only 2 cases with platelet count lower than 20 x10⁹/L were treated with IVIG, with rapid response, although one of these patients suffered an early relapse that needed additional IVIG and corticosteroid therapy, which was followed by total recovery, similar to previous reports.¹⁵ There were no significant hemorrhagic complications in the series.

The mechanism of thrombocytopenia in EBV-induced mononucleosis appears to be peripheral and immune-mediated. In the bone marrow, megakaryocytes are typically normal or increased.^{7,10,16} Antiplatelet antibodies have been detected^{7,16} and platelet-bound IgG¹⁷ in some cases of thrombocytopenia during infectious mononucleosis. In the current series, however, thrombocytopenia was inversely correlated with total serum IgG concentrations. Infection by EBV is restricted to humans, so no experimental models exist. However, experimental infections with the related murine gammaherpesvirus-68 produce a mononucleosis-like illness in mice with reduced platelet count during the early phase due to antibodies induced by the infection.²¹ The response of thrombocytopenia to corticosteroids and IVIG further supports the notion of an immune basis for EBV-induced thrombocytopenia. Moreover, thrombocytopenia tended to be less frequent in patients receiving corticosteroids before admission. The use of corticosteroids for symptom control in infectious mononucleosis is controversial.^{22,23} The most frequent indication for corticosteroids was tonsillitis hindering swallowing, the same reason why many patients received corticosteroid therapy during hospital admission. This therapy, however, was not associated with a more rapid increase in platelet counts between the acute and convalescent periods. Furthermore, the fingerprint of EBV infection is more frequent in patients with chronic immune thrombocytopenia than in controls.^{24,25} Yan et al. reported that the positive rate of EBV-DNA in blood lymphocytes (as detected by quantitative reverse transcription PCR) from patients with chronic immune

thrombocytopenia was higher than that observed in controls.²⁴ Likewise, Wu et al. reported that the positive rate of EBV in the spleen (as detected by immunohistochemistry) from patients splenectomized for chronic immune thrombocytopenia was higher than that observed in controls.²⁵ The history of previous infectious mononucleosis was not reported in these series.^{24,25} Finally, splenic sequestration is another possible mechanism for thrombocytopenia during infectious mononucleosis;⁷ spleen size was negatively correlated with platelet counts in our series. In addition, EBV can interact with platelets,²⁶ and impaired platelet function during the disease has been reported.²⁷

The study has the strengths of sample size and availability of follow-up (retrospective cohort design). As a weakness, the study is observational and retrospective, with inherent drawbacks.²⁸ All patients were adults (older than 15 years) and had been admitted to the hospital. The findings can, therefore, only be applied to patients with infectious mononucleosis of

similar age and severity.

Conclusions. In summary, thrombocytopenia is common in hospitalized patients with severe infectious mononucleosis. Even many patients with normal baseline platelet counts experience an increase during convalescence, suggesting that relative thrombocytopenia can nearly be the rule in EBV-induced infectious mononucleosis. Thrombocytopenia tends to be negatively associated with typical findings of mononucleosis syndrome, such as sore throat, lymphadenopathy, lymphocytosis, and heterophile antibodies. Thrombocytopenia tends to be positively associated with larger spleen size and surrogate markers of disease severity. Most cases of thrombocytopenia are mild, and patients recover spontaneously without needing treatment. Although thrombocytopenia during EBV-induced infectious mononucleosis appears to be immune, more studies would be needed to elucidate its pathogenic mechanisms more precisely.

References:

- Raadsen M, Du Toit J, Langerak T, van Bussel B, van Gorp E, Goeijenbier M. Thrombocytopenia in virus infections. *J Clin Med* 2021;10:877. <https://doi.org/10.3390/jcm10040877> PMID:33672766 PMCID:PMC7924611
- Assinger A. Platelets and infection - an emerging role of platelets in viral infection. *Front Immunol* 2014;5:649. <https://doi.org/10.3389/fimmu.2014.00649> PMID:25566260 PMCID:PMC4270245
- Cohen J. Epstein-Barr virus infection. *N Engl J Med* 2000;343:481-492. <https://doi.org/10.1056/NEJM200008173430707> PMID:10944566
- Godshall SE, Kirchner JT. Infectious mononucleosis. Complexities of a common syndrome. *Postgrad Med* 2000;107:175-186. <https://doi.org/10.1080/19419260.2000.12277439>
- Straus SE, Cohen JI, Tosato G, Meier J. NIH conference. Epstein-Barr virus infections: biology, pathogenesis and management. *Ann Intern Med* 1993;118:45-58. <https://doi.org/10.7326/0003-4819-118-1-199301010-00009> PMID:8380053
- Lennon P, Crotty M, Fenton JE. Infectious mononucleosis. *BMJ* 2015;350:h1825. <https://doi.org/10.1136/bmj.h1825> PMID:25899165
- Pipp ML, Means ND, Sixbey JW, Morris KL, Gue CL, Baddour LM. Acute Epstein-Barr virus infection complicated by severe thrombocytopenia. *Clin Infect Dis* 1997;25:1237-1239. <https://doi.org/10.1086/516114> PMID:9402388
- Zhang C, Kelly AM. Severe thrombocytopenia in a case of Epstein-Barr virus-induced infectious mononucleosis. *Cureus* 2021;13:e17706. <https://doi.org/10.7759/cureus.17706>
- Likic R, Kuzmanic D. Severe thrombocytopenia as a complication of acute Epstein-Barr virus infection. *Wien Klin Wochenschr* 2004;116:47-50. <https://doi.org/10.1007/BF03040424> PMID:15030124
- Walter RB, Hong TC, Bachli EB. Life-threatening thrombocytopenia associated with acute Epstein-Barr virus infection in an older adult. *Ann Hematol* 2002;81:672-675. <https://doi.org/10.1007/s00277-002-0557-1> PMID:12454710
- Pader E, Grossman H. Thrombocytopenic purpura in infectious mononucleosis. *N Y State J Med* 1956;56:1905-1910.
- Carter RL. Platelet levels in infectious mononucleosis. *Blood* 1965;25:817-821. <https://doi.org/10.1182/blood.V25.5.817.817> PMID:14282050
- Cantow EF, Kostinas JE. Studies on infectious mononucleosis. 3. Platelets. *Am J Med Sci* 1966;251:664-667. <https://doi.org/10.1097/0000441-196606000-00005>
- Macswain KF, Higgins CD, McAulay KA, Williams H, Harrison N, Swerdlow AJ, Crawford DH. Infectious mononucleosis in university students in the United Kingdom: evaluation of the clinical features and consequences of the disease. *Clin Infect Dis* 2010;50:699-706. <https://doi.org/10.1086/650456> PMID:20121570
- Cyran EM, Rowe JM, Bloom RE. Intravenous gammaglobulin treatment for immune thrombocytopenia associated with infectious mononucleosis. *Am J Hematol* 1991;38:124-129. <https://doi.org/10.1002/ajh.2830380210> PMID:1951302
- Steeper TA, Horwitz CA, Moore SB, Henle W, Henle G, Ellis R, Flynn PJ. Severe thrombocytopenia in Epstein-Barr virus-induced mononucleosis. *West J Med* 1989;150:170-173.
- Kernoff LM. Demonstration of increased platelet-bound IgG in infectious mononucleosis complicated by severe thrombocytopenia. *Scand J Infect Dis* 1980;12:67-69. <https://doi.org/10.3109/inf.1980.12.issue-1.12> PMID:7367838
- Páez-Guillán EM, Campos-Franco J, Alende R, Garitaonandia Y, González-Quintela A. Transient hypertriglyceridemia: a common finding during Epstein-Barr virus-induced infectious mononucleosis. *Lipids Health Dis* 2021;20:177. <https://doi.org/10.1186/s12944-021-01603-9> PMID:34895245 PMCID:PMC8667370
- Páez-Guillán EM, Campos-Franco J, Alende R, Lázare H, Beceiro C, Gonzalez-Quintela A. Jaundice in relation to immune activation during Epstein-Barr virus-induced infectious mononucleosis. *Am J Med Sci* 2023 (in press). <https://doi.org/10.1016/j.amjms.2022.12.004> PMID:36526005
- Wong SY, Bennett B. Natural history of severe thrombocytopenia in infectious mononucleosis. *Postgrad Med J* 1982;58:249-251. <https://doi.org/10.1136/pgmj.58.678.249> PMID:7111109 PMCID:PMC2426381
- Freeman ML, Burkum CE, Lanzer KG, Roberts AD, Pinkevych M, Itakura A, Kummer LW, Szaba FM, Davenport MP, McCarty OJ, Woodland DL, Smiley ST, Blackman MA. Gamma herpesvirus latency induces antibody-associated thrombocytopenia in mice. *J Autoimmun* 2013;42:71-79. <https://doi.org/10.1016/j.jaut.2012.11.005>

- PMid:23245703 PMCID:PMC3608809
22. Thompson SK, Doerr TD, Hengerer AS. Infectious mononucleosis and corticosteroids: management practices and outcomes. *Arch Otolaryngol Head Neck Surg* 2005;131:900-904.
<https://doi.org/10.1001/archotol.131.10.900>
PMid:16230594
 23. Rezk E, Nofal YH, Hamzeh A, Aboujaib MF, AlKheder MA, Al Hammad MF. Steroids for symptom control in infectious mononucleosis. *Cochrane Database Syst Rev* 2015;2015:CD004402.
<https://doi.org/10.1002/14651858.CD004402.pub3>
PMid:26558642 PMCID:PMC7047551
 24. Yan M, Zhang Y, Yang F, Ji L, Wang M, Wang W. Comparative study between chronic immune thrombocytopenia patients and healthy population on Epstein-Barr virus infection status by polymerase chain reaction. *Expert Rev Hematol* 2020;13:781-786.
<https://doi.org/10.1080/17474086.2020.1772746>
PMid:32498632
 25. Wu Z, Zhou J, Wei X, Wang X, Li Y, Peng B, Niu T. The role of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in immune thrombocytopenia. *Hematology* 2013;18:295-299.
<https://doi.org/10.1179/1607845413Y.0000000084>
PMid:23540727
 26. Nunez D, Charriaut-Marlangue C, Barel M, Benveniste J, Frade R. Activation of human platelets through gp140, the C3d/EBV receptor (CR2). *Eur J Immunol* 1987;17:515-520.
<https://doi.org/10.1002/eji.1830170413>
PMid:2952514
 27. Clancy R, Jenkins E, Firkin B. Platelet defect of infectious mononucleosis. *Br Med J* 1971;11:646-648.
<https://doi.org/10.1136/bmj.4.5788.646>
PMid:5134559 PMCID:PMC1799842
 28. Talari K, Goyal M. Retrospective studies - utility and caveats. *J R Coll Physicians Edinb* 2020;50:398-402.
<https://doi.org/10.4997/jrcpe.2020.409>
PMid:33469615