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Transitory Polyglobulia and Low Platelet Count Associated With Pfizer/ Biontech Mrna Vaccine - A Case Report

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ABSTRACT

The authors report a case of transitory polyglobulia and low platelet count associated with Pfizer mRNA vaccine administration. Upregulation of heme, beta- and gamma-globin synthesis due to activation of NFR2 by IRP/ synthetic mRNA/eIF4E complex and decreased immune-mediated megakaryocytopoiesis and/or peripheral platelet destruction, were hypothesized mechanisms.

Keywords

Low platelet count, Pfizer mRNA vaccine, Polyglobulia.

Abbreviations

ADP: Adenosine Diphosphate; BUN: Blood Urea Nitrogen; COVID-19: Coronavirus disease 2019; NDC: Normal Differential Count; eIF4E: eukaryotic translation initiation factor 4E; FEU: Fibrinogen Equivalent Unit; fT4: free T4; INR: International Normalized Rate; IRE: Iron Response Elements; IREBP: Iron-responsive Element Binding Protein; IRP: Iron Regulatory Proteins; JAK-2: Janus kinase 2; NFR2: Nuclear Factor (erythroid-derived 2)-like 2; PTT: Partial Thromboplastin Time; UTR: 5' untranslated repeats; TSH: Thyroid Stimulating Hormone; WBC: White Blood Count.

Introduction

COVID-19 (coronavirus disease 2019) is a systemic human infection caused by SARS-CoV-2 (severe acute respiratory syndrome-coronavirus 2), declared as a global pandemic by WHO in March 2020. This virus is an airborne agent associated with high transmissibility, morbidity, and lethality rates. Among the many strategies implemented for its prevention, pharmaceuticals worldwide provide novel technology vaccines such as vector DNA and mRNA. Regarding the latter platform, the vaccine antigen (viral spike protein) is artificially coded in an mRNA strand, to be translated into spike protein by the cellular machinery of the vaccinated individual. Among the several available technologies for vaccine mRNA delivery, Pfizer/BioNTech developed a lipid nanoparticle system in which the vaccine mRNA is introduced into the cells of the injected muscle through the fusion of the nanoparticles with their cell membranes [1]. Nevertheless, as with any drug, diagnostic device, or vaccine, Pfizer/BioNTech safety database is continuously under construction. In this paper, we report a case of transitory polyglobulia and low platelet count, temporally associated with Pfizer/BioNTech mRNA vaccine administration, under the patient's signed informed consent.

Case Report

Female, 69 years old, referred on 01.22.2022 to the hematologist due to a hematocrit of 65.9% / hemoglobin 22.4 g/dL (11.23.2021) (complete lab workout shown in the Table). The patient was asymptomatic. She used rosuvastatin (hypercholesterolemia) as the sole regular drug (not related to polyglobulia or thrombocytopenia according to its package insert). She had received the following vaccines for COVID-19: (1) Coronavac (inactivated virus) in 3.2021 and 4.2021 and (2) Pfizer/BioNTech mRNA in 10.15.2021. At the physical exam, the patient showed no plethora; vital signs, as well as heart and lung auscultation, were normal; liver and spleen were not felt; hematopoietic bones were painless under digital compression. Aspirin was prescribed after 1.10.2022 results.

Table 1: Lab workout from an evolutionary perspective.

LAB PARAMETERS	4.2019	11.23.2021	1.10.2022	3.24.2022
Hemoglobin (g/dL) (12 to 16.5)	13.4	22.4	13.7	13.5
Hematocrit (%) (36 to 48)	-	65.9	42.1	43.0
WBC (cells/mm^3) (4,500 to 11,000)	-	3,730 (NDC)	5,700	8,205
Platelets (mm^3) (150,000 to 450,000)	-	106,000	220,000	252,000
Ferritin (ng/mL) (13 to 150)	-	207	-	
D-dimer (ng/mL FEU) (<500)	-	-	649*	632

*Before aspirin prescription.

Further exams yielded the following results (1.10.2022) - (1) BCR-ABL (breakpoint cluster region-Abelson leukemia virus) fusion gene, not detected; (2) JAK-2 (Janus kinase-2) (V617F mutation), not detected (3) platelet aggregation test: a) ristocetin and collagen, normal, and b) ADP and adrenaline, hypoaggregation; (4) normal albumin, BUN, creatinine, erythropoietin, fT4, TSH, globulin, INR, PTT, transferin saturation, vitamin B12, uric acid, and urinalysis; (5) abdominal CT: accessory spleen, possible mesenteric panniculitis, and diverticulosis; and (6) normal chest CT.

The temporality of polyglobulia and low platelet count with Pfizer/BioNTech mRNA vaccine administration, the transitory character of these changes, and the exclusion of other possible causes for both findings made us establish polyglobulia and low platelet count associated with the above vaccine as the most plausible diagnosis. The patient was advised not to take Pfizer/BioNTech mRNA vaccine in the future. On 3.24.2022, the patient had no complaints and her hematological parameters were within reference values, as shown in the Table. Aspirin was continued.

Proposed Underlying Mechanisms for the Findings

The low platelet count found in our case could be explained by peripheral as well as medullary immune-mediated platelets and megakaryocyte destruction, respectively, as a side effect Pfizer/BioNTech mRNA vaccine administration [2,3]. While the basis for the low platelet count was not difficult to figure out, the explanation for the polyglobulia was in turn rather challenging. Therefore, we decided to build up a model based on some aspects of the molecular physiology of normal erythropoiesis and the pharmacodynamics of the Pfizer/BioNTech mRNA vaccine.

Iron regulatory proteins comprise a post-transcriptional feedback system that controls the expression of proteins involved in iron uptake, release, and storage. Knowingly, IRP (iron regulatory proteins) exert their physiologic role through the binding of IREBP (iron-responsive element binding protein) to the ferritin mRNA IRE (iron response elements) located in its UTR (5' untranslated repeats), with NFR2 (nuclear factor [erythroid-derived 2]-like 2) activation as one possible consequence. NFR2 is a transcription factor that has as targets - (1) genes involved in beta- and gamma-globin genes transcription and (2) genes that encode transcription factors for two genes which in their turn encode two proteins involved in heme generation of hemoglobin: (a) ABCB6 (ATP binding cassette subfamily B member 6) (imports porphyrins from the cytosol to the mitochondria) and (b) ferrochelatase (inserts ferrous iron into protoporphyrin IX) [4,5].

elF4E is a protein encoded by a homonymous oncogene, involved in cell cycle regulation through post-transcriptional modulation. Synthetic mRNA present in Pfizer/BioNTech vaccines contains a designed cap followed by sequences of UTR of beta-globin gene, meant to provide a higher affinity for eIF4E (eukaryotic translation initiation factor 4E) binding. The aforementioned bond could artificially increase the mRNA translation rate into the desired spike protein, as well as the stability of the former [6]. We propose that, possibly through a mechanism similar to the IREBP/mRNA IRE detailed above, the complex IRP/synthetic mRNA/eIF4E persistently activates NFR2, therefore upregulating heme, beta- and gamma-globin synthesis. Eventually, this effect wanes as the synthetic mRNA is exhausted. The inferable increase and normalization in hemoglobin synthesis could explain the transitory polyglobulia exhibited by our patient.

Discussion

To the best of our knowledge, this is the first clinical case of polyglobulia and low platelet count associated with Pfizer/BioNTech mRNA vaccine administration, reported in the medical literature. Fortunately, the clinical course of this patient was favorable, suggesting a benign character of the adverse effects possibly related to this vaccine. Polyglobulia and low platelet count due to hyperstimulation of erythropoiesis and immune-mediated megakaryocyte and/or platelet destruction, respectively, were the proposed underlying mechanisms for the phenomenon.

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