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TRANSFUSION

A case of platelet transfusion refractoriness in a CD36-negative patient with acute myeloid leukemia: Diagnostic and therapeutic management

To the Editor,

CD36 deficiency is responsible for CD36 iso-immunizations following pregnancy causing fetal and neonatal alloimmune thrombocytopenia (FNAIT)[1] and sometimes early fetal loss or platelet transfusion, inducing platelet transfusion refractoriness and, in some cases, post-transfusion purpura[2]; We report the case of a 25-year-old man originating from Mali (Africa) treated for acute myeloid leukemia secondary to treatment for Hodgkin's lymphoma. The patient received induction course with idarubicin (9 mg/m^2 from day [D] 1 to day 5) and cytarabine (200 mg/m^2 from D1 to D7), inducing aplasia. Because two platelet transfusions with a dose $>0.5 \times 10^{11}$/kg of patient weight were ineffective, HLA and HPA alloantibodies were screened. The anti-HLA antibody screening (One Lambda, Inc., Canoga Park, CA) by the Luminex technique and the anti-HPA antibodies by MAIPA (Monoclonal Antibody-specific Immobilization of Platelet Antigens, ApDia, Turnhout, Belgium) were negative. Surprisingly, anti-CD36 iso-antibodies (iso-Abs) using a bead-based multiplex assay PakLx (Immucor, Waukesha, WI) were detected with an MFI (mean fluorescence intensity) of 5236. A reference laboratory (HPA/HLA Laboratory, EFS Bretagne, Rennes, France) confirmed the detection of CD36 iso-Abs using MAIPA with clone FA6.152 anti-CD36 Moab. Homemade sequencing highlighted a mutation in exon 12 of the CD36 gene, NM_000072.3:c.975T > G, inducing a stop codon at position 325 of the mature protein, already recorded as rs567787470 in the international database. To limit inefficiency platelet transfusion, three strategies were developed during his treatment. The different strategies and platelet concentrates transfused following the chronological order of the treatment sequences are described in Table 1.

TABLE 1 Transfusion effectiveness

Chemotherapy course	Product	ABO group	Date of transfusion	Platelet numeration before transfusion (G/L)	Platelet numeration after 24 h transfusion (G/L)	Platelet dose transfused (10^{11})	24 h CCI
Induction	Apheresis	O	0	17	32	3.66	7.03
	BCP	O	4	8	19	3.2	5.9
	BCP	O	5	3	3	4	0
	BCP	O	6	3	3	5.7	0
	BCP	O	7	3	3	6.8	0
	BCP	O	8	3	3	7	0
	BCP	O	9	3	3	3.7	0
First consolidation	BCP	O	39	14	9	7.2	−1.19
	BCP	O	40	9	7	6.5	−0.53
Second consolidation	Apheresis£	O	104	11	63	4.93	18.1

Abbreviations: BCP, buffy-coat pool; G/L, giga per liter; £, compatible donor.

TABLE 2 Monitoring (MFI) of CD36 antibodies by Luminex in the desensitizing protocol (positive cut-off MFI value >1000)

	Therapeutic setting	Day after first transfusion	Serum undiluted (MFI)	Serum dilution (MFI)					
				1/10	1/50	1/100	1/200	1/400	1/500
Desensitization	Diagnosis	6	5,326						
	Rituximab	83	6,335	4,025	2,072	1,089	856		218
	Before PP	87	7,015		5,351	4,046	1,768	1,073	
	After PP	87	5,144		2,755	1,557	682	348	
	Bortezomib	89	12,727		4,269	2,869	1,443	687	
	After PP	90	9,418		1,925	914	446	192	
Follow-up		93	9,839		3,187	1,812	692	356	
		102	10,075		3,114	2,124	1,269	613	
		138	9,335		3,189	1,724	1,105	456	318

Abbreviations: MFI, mean fluorescence intensity; PP, Plamapheresis.

The first strategy was based on searching for CD36– blood donors. These donors were selected from the French registry based on their erythrocyte phenotype of African origin D + C − E − c + e + Fya − Fyb. Three hundred thirty-four donors were called to be included in the screening program. Among the 27 donors tested (7% of contacted donors) using the MAIPA method, only one (4%) was CD36 negative. CD36 gene sequencing revealed a mutation in exon 12, already described and recorded as rs3211938 in the international database. Platelet collection of this donor was performed only before the second consolidation cure. Unfortunately, this donor no longer agreed to donate. Thus, in the absence of compatible platelet products for the first course, the decision was made not to transfuse platelet products except in cases of bleeding complications. Thus, two autologous platelet concentrates were collected for curative therapy after the first hematological recovery and were stored frozen before the second consolidation. Because neither case bleeding complication occurred, these concentrates were not used. In parallel, a desensitization protocol has been implemented with rituximab, bortezomib (Velcade), proteasome inhibitor, and plasmapheresis (PP) for anti-CD36 Ab suppression.[3] CD36 antibody quantification was performed by Luminex PakLx on serum samples drawn both pre- and/or post-PP for the determination of anti-CD36 Ab strength (MFI). The strength of anti-CD36 Ab slowly decreased over the course of the treatment, with an MFI from 850 for a 1/200 serum dilution to 914 for a 1/100 dilution (Table 2). This variation was not considered sufficiently effective to transfuse the patient with incompatible platelets. Three days after the last PP, the MFI was similar to that at the start of the CD36 desensitizing protocol, thus showing that Ab production was strong and continuous. Thus, the second consolidation cure with prior CD36 desensitization was followed by a transfusion from a compatible donor to limit the risk of bleeding complications. The transfusion was effective, and the aplasia lasted 10 days without bleeding complications. After the third consolidation, no platelet product was transfused, and no bleeding complications occurred during aplasia. Two years later, the patient is still in complete remission from the acute leukemia. In conclusion, this case illustrates the difficulty in France of managing platelet inefficiencies in patients with anti-CD36 isoimmunization. The inefficiency of the desensitization procedure leads to a priority search for blood donors deficient in CD36, potentially in a registry of CD36 phenotyped blood donors in Europe or to use other therapeutic strategy such effector silencing monoclonal antibody against CD36[4]; The screening for CD36 deficiency in blood donor can be facilitated by using flow cytometry instead to MAIPA.[5]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Pascal Pedini[1,2]
Yosr Hicheri[3]
Gerald Bertand[4]
Isabelle Dettori[1]
Agnes Basire[1]
Catherine Lazaygues[1]
Corinne Chabrières[1]
Camille Perrin[1]
Jeanne Pascal[1]
Jacques Chiaroni[1,2]
Virginie Renac[4]
Patrick Ladaique[3]
Norbert Vey[3,5]
Christophe Picard[1,2]

[1]EFS PACA-Corse, Marseille, France
[2]UMR 7268 ADÉS Aix-Marseille Université/EFS/CNRS, Marseille, France
[3]Department of Hematology, Institut Paoli-Calmettes, Marseille, France
[4]Immunology Platelet Laboratory, EFS Bretagne, Rennes, France
[5]Aix-Marseille Univ, Inserm, CNRS, Institut Paoli-Calmettes, CRCM, Marseille, France

Correspondence
Pascal Pedini, UMR 7268 ADÉS Aix-Marseille Université/EFS/CNRS, Marseille, France.
Email: pascal.pedini@efs.sante.fr
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ORCID
Pascal Pedini https://orcid.org/0000-0001-9299-3705

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Neutralization profile of SARS-CoV-2 omicron BA.1 variant in high binding titer plasma

The SARS-CoV-2 B.1.1.529 or Omicron variant has shortened the list of antibody therapeutics against COVID-19. Many spike protein-directed monoclonal antibodies do not have neutralization capacity against Omicron's subvariants BA.1 and BA.2.[1,2] Given this constantly changing antigenic landscape, high-titer convalescent plasma (HT-CCP) could regain its role as a frontline therapy for COVID-19. However, some early in vitro evidence suggests that HT-CCP collected during previous waves of COVID-19 may not be effective against Omicron.[3]

In this retrospective study, we evaluated the neutralizing capacity (i.e., neutralizing antibody concentrations) against SARS-CoV-2 Omicron BA.1 variant in high binding antibody concentration plasma samples obtained from subjects with diverse exposure to SARS-CoV-2 through infection, vaccination, or both. The plasma samples were obtained from Vilnius University Hospital Santaros Klinikos Biobank (Vilnius, Lithuania). All participants had signed a written, informed consent for biobanking. The study was approved by Vilnius Regional Bioethics Committee (approval number 2021/5-1342-818).

The plasma samples were collected from healthy health-care workers who had been vaccinated by three doses of BNT162b2 (Comirnaty, Pfizer-BioNTech) or mRNA-1273 (Spikevax, Moderna) vaccines (Group 1); healthy plasma donors who had been infected with B.1.351 (Delta) variant of SARS-CoV-2 and received at least one dose of the BNT162b2 or mRNA-1273 vaccine (Group 2); and from Omicron infected healthy health-care workers who had received at least one dose of the aforementioned vaccines (Group 3). Specimens from the latter two groups were obtained at least 3 weeks after positive SARS-CoV-2 PCR test during either Delta or Omicron BA.1 waves of infection in Lithuania, respectively. Samples with binding antibody concentrations greater than 1000 BAU/ml (≥7041 AU/mL) using Abbott Architect SARS-CoV-2 IgG Quant II chemiluminescent microparticle immunoassay (Abbott, Sligo, Ireland) were considered as having high-titer plasma. High binding antibody samples were then analyzed with cPass SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript, Piscataway, New Jersey, USA) RBD-ACE2 competition assay using Omicron's BA.1 antigen.