Persistence of functional anti-PF4 antibodies and neutrophil activation in vaccine-induced immune thrombotic thrombocytopenia

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ABSTRACT

Background: Vaccine-induced immune thrombotic thrombocytopenia (VITT) is characterized by thrombocytopenia and thrombosis in unusual sites triggered by anti-PF4 antibodies. To the best of our knowledge no studies with very long follow-up on anti-PF4 antibodies persistence have been reported.

Methods: We carried out a multicenter study in 16 VITT patients studied at T0 (acute episode), T1 and T2 (after 6 and 29 months) assessing the persistence of anti-PF4/heparin antibodies and of neutrophil activation.

Results: At T0 80%, at T1 75%, and at T2 11% of VITT patients were positive for anti-PF4/heparin antibodies by ELISA, while 75% at T0, 56% at T1, and 0% at T2 had a positive platelet activation assay. Plasmatic MMP-9 and MMP-9/NGAL were strikingly elevated at diagnosis, but they normalized at T1. No clinical relapses were observed.

Conclusions: Although anti-PF4 antibodies may persist for a long-time following an acute VITT episode, they seem to be clinically irrelevant.

Introduction

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare but life-threatening syndrome initially described as a complication of adenoviral (Ad) vector anti-COVID-19 vaccines and characterized by thrombosis in unusual sites (most frequently cerebral venous sinus - CVST- and splanchnic vein thrombosis - SVT), often associated with multiple venous and/or arterial thromboses, thrombocytopenia, strongly increased circulating D-dimer levels and positivity for anti PF4 antibodies, occurring 5-30 days after vaccination.[1-3] Besides platelet activation, a strong stimulation of neutrophils has also been reported in VITT patients with the formation of neutrophil extracellular traps (NETs).[4] More recently, new VITT-like disorders sharing with VITT thrombocytopenia, markedly raised D-dimer levels, platelet

activating anti-PF4 antibodies and unusual site thrombosis, have been described following the administration of other vaccines, like Gardasil 9 for human papillomavirus (HPV) and mRNA-based Covid-19 vaccines, during bacterial or viral respiratory infections, and in patients with a monoclonal gammopathy of undetermined significance.[5,6]

Thrombotic events in VITT are due to the generation of anti-PF4 antibodies activating platelets and neutrophils through FcγRIIA.[1] Anti-PF4 antibodies persist for some time after an acute VITT episode with differences depending on the assay used.[7,8]

In fact, anti-PF4 antibodies were reported to persist in 94.3% of VITT patients at a median follow-up of 3 months in one study (range: 4 to 19 weeks),[9] in 72% of VITT patients at a median follow-up of 3.5 months in another (range: 5 to 23 weeks),[8] in 78.5% and in 77.7% of VITT patients at a median 6 month follow-up in a third (range: 3 to 36 weeks) and a fourth (range: 24 to 29 weeks) study,[10,11] in 100% of VITT patients at a median 7 month follow-up in a fifth (range: 28 to 40 weeks),[12] and in 55% of VITT patients at a median follow-up of 20 months (range: 13 to 99 weeks) in a sixth study,[13] using different assays. However, the ability of the residual antibodies to activate platelets was reported only in few VITT patients, for instance in 34% of VITT patients at a median follow-up of 3 months,[9] in 42.8% at a median 5 month follow-up,[12] in 26% and 11% at a median 6 month follow-up,[10,11] and in 8.5% at a median follow-up of 20 months,[13] using different platelet-activating assays. To the best of our knowledge, no studies with longer follow-up have been reported to date.

Besides anti-PF4 antibodies, some studies showed that the autoimmune response triggered by Ad-vector vaccines involves the development of autoantibodies against platelet surface glycoproteins,[14-18] but no studies have assessed the persistence of these antibodies after an acute VITT episode.

Finally, acute VITT is associated with a strong neutrophil activation with NET formation. NET biomarkers were shown to persist for at least 6 months in patients previously hospitalized for COVID-19, and to be linked to pulmonary fibrosis, cardiovascular abnormalities, and neurological dysfunction in long COVID.[19] Also MMP-9 was significantly elevated in the serum of long COVID patients compared to healthy controls.[20] To the best of our knowledge, no data have been reported on the possible persistence of neutrophil activation in patients with a previous VITT. Anti-PF4 persistence and their platelet and neutrophil activating activity may be important in the decision about anticoagulant treatment duration and in the estimate of the risk of relapse, thus a more precise definition of this issue may facilitate the identification and management of potential sequelae.

We carried out a multicenter study in 16 patients who survived an acute VITT episode to evaluate the persistence of anti-PF4/heparin antibodies and their platelet-activating activity, of antiplatelet autoimmunity, and of neutrophil activation.

Materials and Methods

Patients

Sixteen patients who survived an acute VITT event were enrolled in a multicenter study involving 14 Italian centers.[21] Fourteen out of 16 VITT patients (87.5%) suffered VITT after ChAdOx1 administration, while 2 out of 16 (12.5%) following Ad26.COV2.S. The section of Internal and Cardiovascular Medicine of the University of Perugia centralized samples and analysis. The study was approved by the local Ethics Committees (CER Umbria n. 3656/20 and the Bioethics Committee of University of Perugia n. 222848) and each study participant or their legally authorized representative gave written informed consent. Demographic and clinical variables were collected at enrollment, as well as all the relevant clinical and laboratory data on the VITT episode. VITT was classified as definite or probable according to the consensus diagnostic criteria for VITT developed by the UK Haematology Expert Group.[22] VITT patients were studied at three time points: on the day of VITT diagnosis (T0), after an average of 6.2±2 months (min-max 72-284 days) (T1), and after an average of 29±1 month (min-max 812-894 days) (T2). At T1 16 patients were studied (100%), while at T2 9 out of 16 VITT patients were recruited (56%). Thirty-one age- and sex-matched healthy volunteers who underwent anti-SARS-CoV-2 vaccine administration without suffering from VITT were also enrolled.

Samples

Peripheral venous blood was collected either in 0.18% K3EDTA, or in trisodium citrate 3.2% (0.109 M, 1/10 v/v), or in non-anticoagulated glass tubes. Platelet-poor plasma (PPP) was obtained by centrifuging whole blood at 4,000xg for 10 min; while serum was obtained from non-anticoagulated whole blood kept at 37°C for 60 min and then centrifuged at 4,000xg for 10 minutes. Samples were divided in small aliquots and stored at –80°C for later assays.[15,23]

Anti-PF4/heparin antibodies

At T0 anti-PF4/heparin antibodies were searched using two different enzyme linked immunosorbent assays, the PF4 enhanced assay (Immucor, Dreieich, Germany) and the Asserachrom HPIA assay (Diagnostica Stago, Inc., Parsippany, NJ, USA), or by a chemiluminescence assay (AcuStar HIT-IgG; Werfen, Bedford, MA, USA).[15] At T1 and T2, anti-PF4/heparin antibodies were assessed by two different ELISAs, Immucor and Diagnostica Stago.[15] For Immucor results showing O.D. values ≥0.400, for Stago O.D. values ≥25.5% of the O.D. value obtained for Reagent 6 in the same test-run, and for AcuStar >1.00 U/mL, were considered positive.

Platelet activation

At T0, the ability of anti-PF4/heparin antibodies to activate platelets was tested by different functional assays (heparin□induced multiple electrode aggregometry-HIMEA, platelet aggregation test-PAT, platelet expression assay-PEA, PF4-induced flow cytometry-based platelet activation assay-PIFPA) depending on the test used at each enrolling center, while at T1 and T2 they were centrally assessed by PIFPA, as previously reported.[15]

Antiplatelet autoantibodies

Antiplatelet autoantibodies were searched in serum by the MAIPA assay using the PakAuto® ELISA kit (Immucor GTI Diagnostics Inc., Waukesha, WI, USA).[15] Results showing O.D. values ≥ twice the mean value of negative controls for the corresponding glycoprotein (2 negative controls for each glycoprotein) were considered positive.[15]

Plasmatic MMP-9, MMP-9/NGAL

Plasmatic matrix metalloproteinase-9 (MMP-9) and its heterodimer with NGAL (MMP-9/NGAL), which are neutrophil degranulation markers, were measured by zymography, as previously described.[23,24]

Statistical analysis

Categorical data were analyzed with the Fischer's exact test. The other data were tested for normality distribution with the D'Agostino-Pearson normality test. Data not normally distributed were analyzed with the Mann Whitney test; otherwise, data were analyzed with the two-tailed unpaired Student's *t*-test. Multiple comparisons were performed with one-way ANOVA, followed by the Dunn's or Holm-Sidak's post-tests, where appropriate. Data are reported as means ±SEM. A p-value <0.05 was considered statistically significant. All analyses were performed using the GraphPad Prism 10.4.1 for Windows software (GraphPad Software, San Diego, CA, USA; www.graphpad.com).

Results

Patient characteristics

Clinical and demographic characteristics of enrolled VITT patients and healthy volunteers are reported in Table 1. Patient's age was 51.6±3.1 years (range, 33-73 years), and 43.7 % were males. Fourteen out of 16 VITT patients (87.5%) suffered VITT after ChAdOx1 administration, while 2 out of 16 (12.5%) following Ad26.COV2.S. Eleven out of 16 patients (68.75%) were classified as definite VITT, and 5 (31.25%) as probable.[22]

Anti-PF4/heparin antibodies

At T0, 12 out 15 VITT patients (80%) were positive for anti-PF4/heparin antibodies by ELISA (8 tested with Immucor, 3 with Diagnostica Stago, and 1 with AcuStar), 3 (19%) were negative (2 tested with Stago and 1 with AcuStar), while for 1 (6%) anti-PF4 result was not available. At 6-month follow-up (T1), 9 out 12 VITT patients with positive anti-PF4 immunological test at T0 (75%) were still positive with at least one out of the two different ELISAs performed, in particular 2 out of 12 (17%) only with Diagnostica Stago, 6 out 12 (50%) only with the Immucor assay, and 1 out of 12 patients (8%) with both assays. At 2.4-year follow up (T2) 1 out of 9 patients (11%) still tested weakly positive with the Immucor ELISA (O.D.=0.562, cut-off=0.400). While these results confirm that significant differences exist in anti-PF4 antibody persistence depending on the immunological assay used,[7,8] confirming the need to carry out more than one immunological test for anti-PF4 detection in VITT, they also show that anti-PF4 positivity can persist in some patients for a long time after the acute episode. On the other hand, a progressive and striking decrease of the intensity of anti-PF4/heparin positivity (O.D. values) from the acute VITT episode was observed (T0: median 2.55 and IQR: 1.98-2.72; T1: median 0.55 and IQR: 0.20-0.89; T2: 0.25 and IQR: 0.14-0.43) (Figure 1A), in accordance with previous short term follow-up studies.[9,12]

Platelet activation

At T0, 9 out of 12 VITT patients positive for anti-PF4 by ELISA (75%) had a positive functional platelet activation assay, while the test was not available for 3 (25%) (Figure 1B). At T1, 5 out of 9 anti-PF4 positive VITT patients (56%) still had a positive functional platelet activation assay, while at T2, the single VITT

Table 1. Clinical and demographic characteristics of the study population.

	VITT patients (n=16)	Healthy subjects (n=31)	p-value
Age (years)	51.63±3.21	50.42±2.13	NS
Males (n)	7	13	NS
Vaccine ChAdOx1 (n)	14	28	NS
Vaccine Ad26.COV2.S (n)	2	3	NS
Previous SARS-Cov-2 infection (n)	0	0	NS
Definite VITT (n)	11	NA	NA
Probable VITT (n)	5	NA	NA
Comorbidities			
Hypertension (n)	6	3	p<0.05
Type 2 diabetes mellitus (n)	1	0	NS
Obesity (n)	1	0	NS
Smoke (n)	2	6	NS
Atrial fibrillation (n)	0	0	NS
Chronic respiratory disease (n)	0	0	NS
Kidney failure (n)	1	0	NS
Stroke (n)	0	0	NS
Dyslipidemia	1	2	NS
Peripheral artery disease (n)	1	0	NS

Results are reported as mean ±SEM if not differently indicated; NS, not significant; NA, not applicable.

patient still positive for anti-PF4/heparin antibodies had a negative functional platelet activation assay (Figure 1B).

Antiplatelet autoantibodies

Besides anti-PF4 antibodies, 28%, 12% and 11% of VITT patients were positive for anti-platelet autoantibodies at T0, T1 and T2 respectively. However, anti-platelet autoantibodies did not seem to be of clinical significance, given that all the positive patients had normal platelet counts at T1 and T2.

Plasmatic MMP-9 and MMP-9/NGAL

Plasmatic MMP-9 and MMP-9/NGAL, two neutrophil degranulation markers, were significantly higher in VITT patients at diagnosis compared to healthy subjects (HS), returning to normal levels already at 6 month follow up (T1) (Figure 2 A,B). Moreover, plasmatic MMP-9 and MMP-9/NGAL positively and significantly correlated with the O.D. value of anti-PF4/heparin antibodies (r= 0.53; $p<0.01$; r= 0.42; $p<0.05$).

Rate of relapse

None of the VITT enrolled patients had relapses of either thrombocytopenia or thrombosis during the follow-up. However, one patient reported recurring headaches, accompanied by expressive language difficulties (an inability to fluently articulate concepts) and deficit in the retrieval of common lexical items. Another patient experienced mild dyslexia, which hindered her ability to read accurately and fluently. Additionally, one patient died from an unknown cause, having previously exhibited a rapid and progressive cognitive decline.

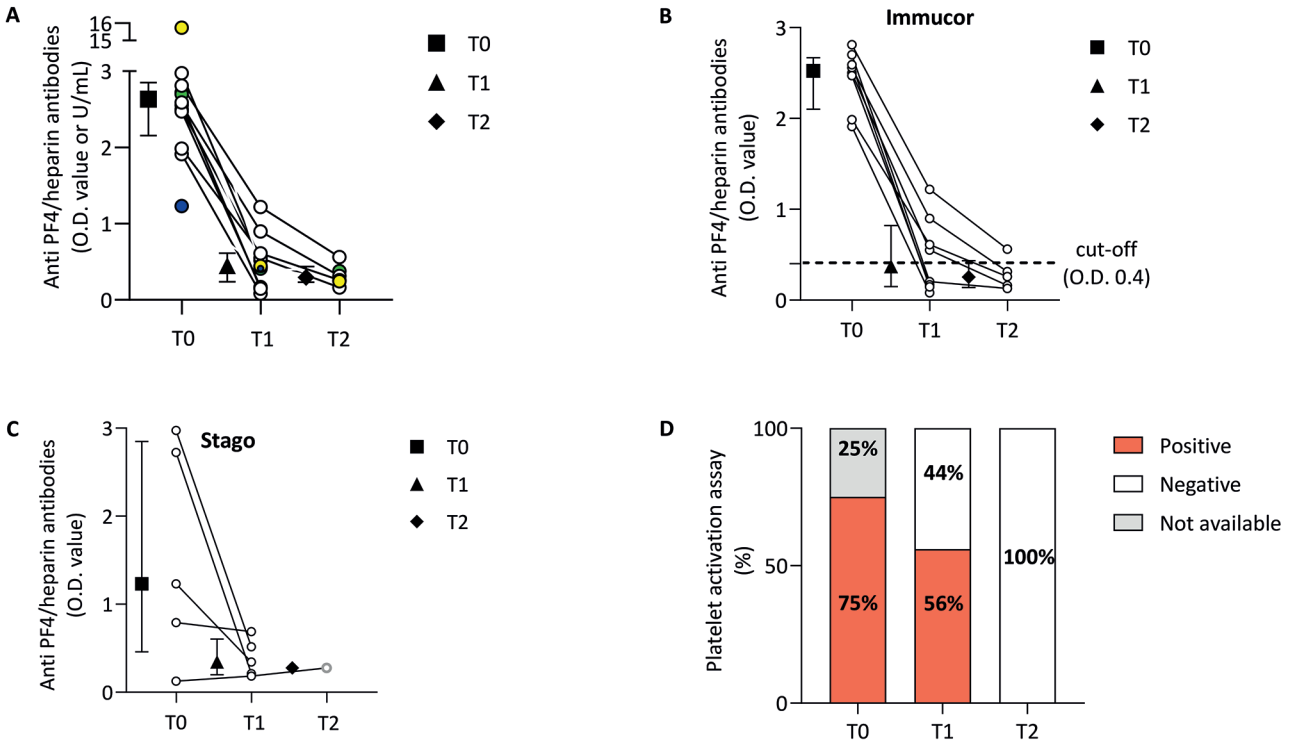

Figure 1. Persistence of functional anti-PF4 antibodies over time in VITT. **A)** Individual PF4/polyanion values of 12 out of 15 VITT patients positive for the presence of anti-PF4/heparin antibodies at acute VITT episode with any of the 3 used assays, Immucor, Diagnostica Stago or Acustar, are shown; each patient is identified by a point; when anti-PF4 antibody detection was performed with the same assay across the three different time points, the corresponding data points are connected by lines, otherwise they are not although they refer to the same individual; however, to facilitate identification, we used a consistent color for each patient across all time points; data are reported as O.D. (for patients in which the presence of anti-PF4 antibodies was assessed by Immucor and Diagnostica ELISA) or U/mL (for patients in which the presence of anti-PF4 antibodies was assessed by Acustar); anti-PF4/heparin values decrease at follow-up as indicated by the reported median with interquartile range (black square at T0, black triangle at T1 and black rhombus at T2). **B)** Individual PF4/polyanion values of 8 out of 16 VITT patients for which the presence of anti-PF4/heparin antibodies was tested with the Immucor assay both at T0, T1 and T2; data are reported as O.D; anti-PF4/heparin O.D. values decrease at follow-up as indicated by the reported median with interquartile range (black square at T0, black triangle at T1 and black rhombus at T2). **C)** Individual PF4/polyanion values of 5 out of 16 VITT patients for which the presence of anti-PF4/heparin antibodies was tested with the Diagnostica Stago assay both at T0, T1 and T2; data are reported as O.D; anti-PF4/heparin O.D. values decrease at follow-up as indicated by the reported median with interquartile range (black square at T0, black triangle at T1 and black rhombus at T2). **D)** Anti-PF4 antibodies activating platelets over time. Percentage of VITT patients with positive (in red), negative (in white) or not available (in purple) functional platelet activation assay.

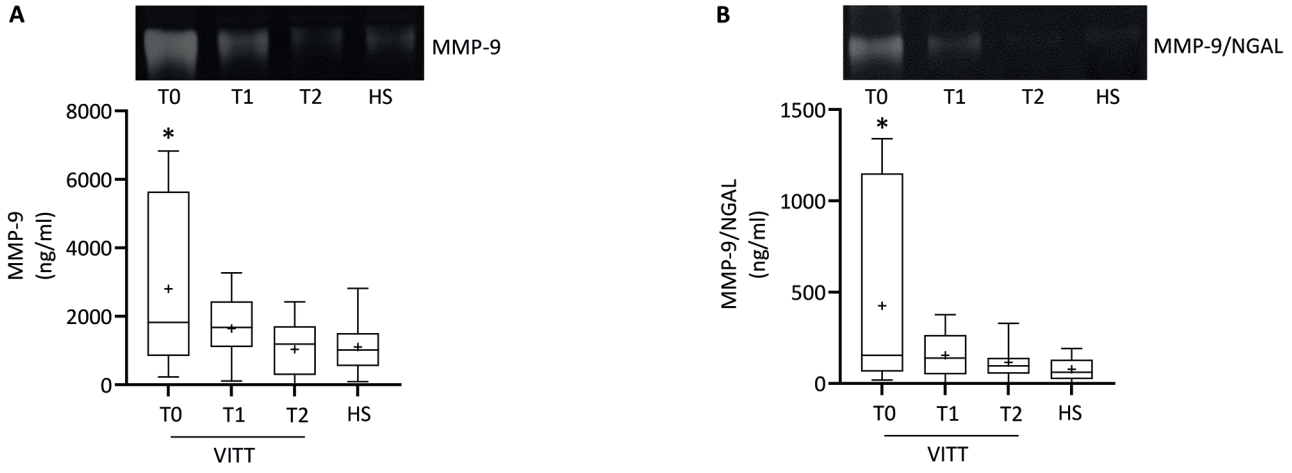

Figure 2. Persistence of neutrophil activation over time in VITT. **A)** Plasmatic MMP-9 levels were quantified by zymography; the inset shows representative zymography of plasmatic MMP-9 in VITT patients at the acute VITT episode, and at two follow up time points (T1: 6 month follow up, and T2: 2.4 year follow up), and in age- and sex-matched healthy controls; one-way ANOVA, followed by the Tukey's multiple comparison test; *p<0.05 *vs* HS + = mean. **B)** Plasmatic MMP-9/NGAL levels were quantified by zymography; the inset shows representative zymography of plasmatic MMP-9/NGAL in VITT patients at the acute VITT episode, and at two follow up time points (T1: 6 month follow up, and T2: 2.4 year follow up), and in age- and sex-matched healthy controls; one-way ANOVA, followed by the Tukey's multiple comparison test; *p<0.05 *vs* HS + = mean.

Discussion

Our data show that in patients with a previous acute VITT episode anti-PF4/heparin antibodies persist long: in 75% of cases at 6 months and still in 11% at 2.4 years, when assessed by an immunological assay (ELISA), but that a progressive and striking decrease in the intensity of antibody positivity occurs. Notwithstanding, at 6-month follow-up anti-PF4 antibodies still induced platelet activation in 56% of cases, whereas at 2.4 years no VITT patients exhibited a positive response in the functional platelet activation assay. Our findings corroborate previous evidence indicating a decline in the platelet-activating capacity of anti-PF4 antibodies, despite their persistence, although previously reported in shorter follow-ups.[9-13] The exact causes of anti-PF4 antibody persistence in some subjects are still largely unknown and may be due to a large extent to differences in immune responses. In fact, the available evidence suggests the existence of two antibody profiles in VITT patients: those whose platelet-activating antibody levels decrease over time and those with persistent platelet-activating antibodies.[25] However, even in patients with persistence of platelet-activating antibodies, neither thrombotic nor thrombocytopenic relapses were observed either in our cohort, or in previous reports,[8,10,12,13] suggesting their clinical irrelevance. Thus, our study, that to the best of our knowledge is the first evaluating the persistence of anti-PF4 antibodies at >2 years follow-up, shows that anti-PF4 antibodies persist long after an acute VITT episode, but that they lose their platelet activating ability, as well as their clinical significance.

We also observed that the persistence of anti-PF4 antibodies depends on the immunological assay used, confirming the need to carry out more than one immunological test for anti-PF4 detection in VITT.[7,8]

Besides anti-PF4 antibodies, at T0 28% of patients were also positive for anti-platelet autoantibodies, confirming previous results,[14] and, similar to anti-PF4/heparin antibodies, they decreased over time. However, anti-platelet autoantibodies did not seem to be of clinical significance, given that they were reported also in 34% of patients who underwent adenoviral-vector anti SARS-CoV-2 vaccination without suffering from VITT,[15] and that in our case series they did not associate with thrombocytopenia in the follow-up.

A novel aspect of our study is the analysis of plasmatic markers of neutrophil activation[24] in the long-term follow-up of VITT patients. Both MMP-9 and MMP-9/NGAL were strikingly elevated at diagnosis compared to healthy subjects. Moreover, their plasmatic levels correlated with anti-PF4 O.D. values, in accordance with previous data reporting the synergistic role of platelets and neutrophils in VITT immunopathogenesis.[26,27] However, they normalized already at the 6 months follow-up.

We recognize that our study has some limitations. First, the small number of VITT patients enrolled; however VITT is a rare event with an estimated incidence ranging from 3.2 to 16.1 cases every 100,000 vaccinated subjects for ChAdOx1 nCoV-19, and 1.7 to 3.7 cases for Ad26.COV2.S) and, similarly, previous studies on anti-PF4 antibody-persistence in VITT were performed in small cohorts.[9,11,28] Second, the relatively high fraction of patients lost at the second follow-up, however, at least at 6 months the case series was still reasonably consistent. Finally, the fact that anti-PF4/heparin antibodies and the assessment of their platelet-activating activity were conducted using a variety of assays, since laboratory investigations during the acute VITT episode were performed independently at each participating center without central coordination. However, all the assays at T1 and T2 were performed by one centralized laboratory, enhancing the comparability of results.

In conclusion, our results suggest that the immunological ab-

normalities underlying VITT although persistent seem to be clinically irrelevant, however long-term monitoring could be beneficial for identifying and managing possible sequelae.[29] Elucidating the mechanisms behind this persistence is crucial for the targeted long-term monitoring and effective management strategies of VITT patients.

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