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CONGRÈS DE LA SOCIETE FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE
30 SEPT. 02 OCT. 2026

Une gammapathie monoclonale : une étiologie rare de VITT-like (ou HIT-like) syndromes ?

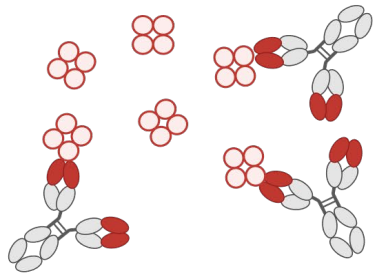
Yves GRUEL- Tours

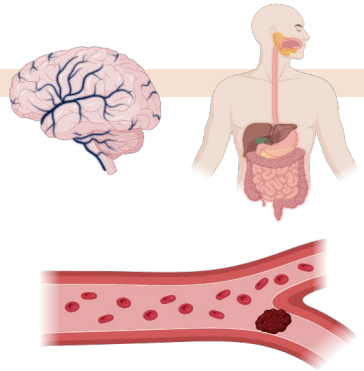
« VITT-like » Syndromes: several causes…



No heparin
No vaccine against COVID-19

Anti-PF4 antibodies similar to VITT antibodies





Thrombocytopenia & atypical thromboses

Viral Infections

Anti-PF4 immunothrombosis without proximate heparin or adenovirus vector vaccine exposure

blood

Linda Schönborn,[1,*] Olga Esteban,[2,*] Jan Wesche,[1] Paulina Dobosz,[2] Marta Broto,[2] Sara Rovira Puig,[2] Jessica Fuhrmann,[1] Raquel Torres,[2] Josep Serra,[2] Roser Llevadot,[2] Marta Palicio,[2] Jing Jing Wang,[3] Tom Paul Gordon,[3] Edelgard Lindhoff-Last,[4] Till Hoffmann,[5] Lorenzo Alberio,[6] Florian Langer,[7] Christian Boehme,[8] Eugenia Biguzzi,[9] Leonie Grosse,[10] Matthias Endres,[11-14] Thomas Liman,[12,13,15] Thomas Thiele,[16] Theodore E. Warkentin,[17] and Andreas Greinacher[1]

The NEW ENGLAND JOURNAL of MEDICINE

Adenovirus-Associated Thrombocytopenia, Thrombosis, and VITT-like Antibodies

Theodore E Warkentin [1], Jacquelyn Baskin-Miller [2], Alison L Raybould [3], Jo-Ann I Sheppard [4], Mercy Daka [4], Ishac Nazy [4], Stephan Moll [2]

Other adenoviral vaccine (VITT rather than VITT-like)

American Journal of Hematology AJH

Human papilloma virus vaccine and VITT antibody induction

Adam J. Kanack, Ingvild J. Lægreid, Silje Johansen, Håkon Reikvam, Maria T. Ahlen, Anand Padmanabhan

Surgery (TKR) (« spontaneous HIT »)

Classification of Platelet-Activating Anti-Platelet Factor 4 Disorders

Int J Lab Hematol, 2025

Theodore E. Warkentin[1,2]

« Monoclonal Gammopathies »

The NEW ENGLAND JOURNAL of MEDICINE

VITT-like Monoclonal Gammopathy of Thrombotic Significance

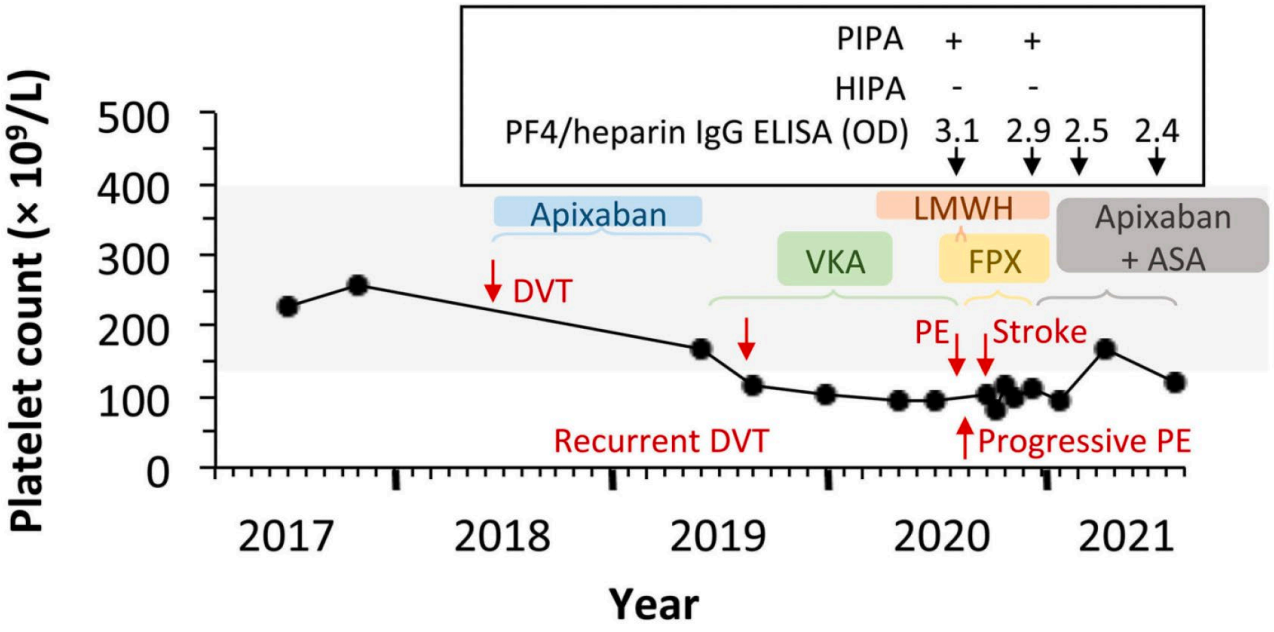
Authors: Jing Jing Wang, Ph.D., Theodore E. Warkentin, M.D., Linda Schönborn, M.D., Matthew B. Wheeler, M.D., William H. Geerts, M.D., Nathalie Costedoat-Chalumeau, M.D., Ph.D., Nicolas Gendron, Pharm.D., Ph.D., Gabriela Ene, M.D., Ph.D., Miquel Lozano, M.D., Ph.D., Florian Langer, M.D., Edelgard Lindhoff-Last, M.D., Kathrin Budde, Ph.D., Tim Chataway, Ph.D., Alexander Troelnikov, M.B., B.S., Jo-Ann I. Sheppard, B.Sc., Yi Zhang, M.Sc., Donald M. Arnold, M.D., Tom P. Gordon, M.D., Ph.D., Thomas Thiele, M.D., Andreas Greinacher, M.D., and Ishac Nazy, Ph.D.

Platelet-activating anti-PF4 antibodies mimic VITT antibodies in an unvaccinated patient with monoclonal gammopathy

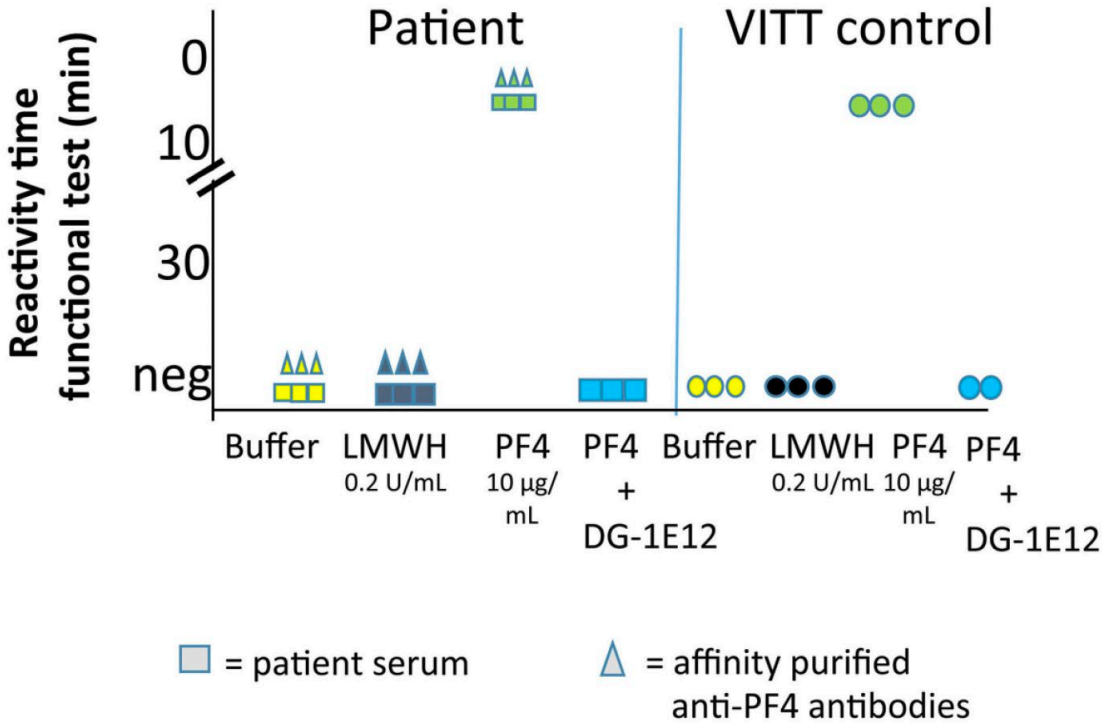
Haematologica, 2022

Andreas Greinacher, Florian Langer, Linda Schonborn, Thomas Thiele, Munif Haddad, Thomas Renne, Jerome Rollin, Yves Gruel, Theodore E. Warkentin

- *German patient with a **chronic disorder** characterized by **thrombocytopenia** and **recurrent thrombosis** refractory to anticoagulation.*



***June 2021: Monoclonal gammopathy IgG κ** (SPEP/IFE)*

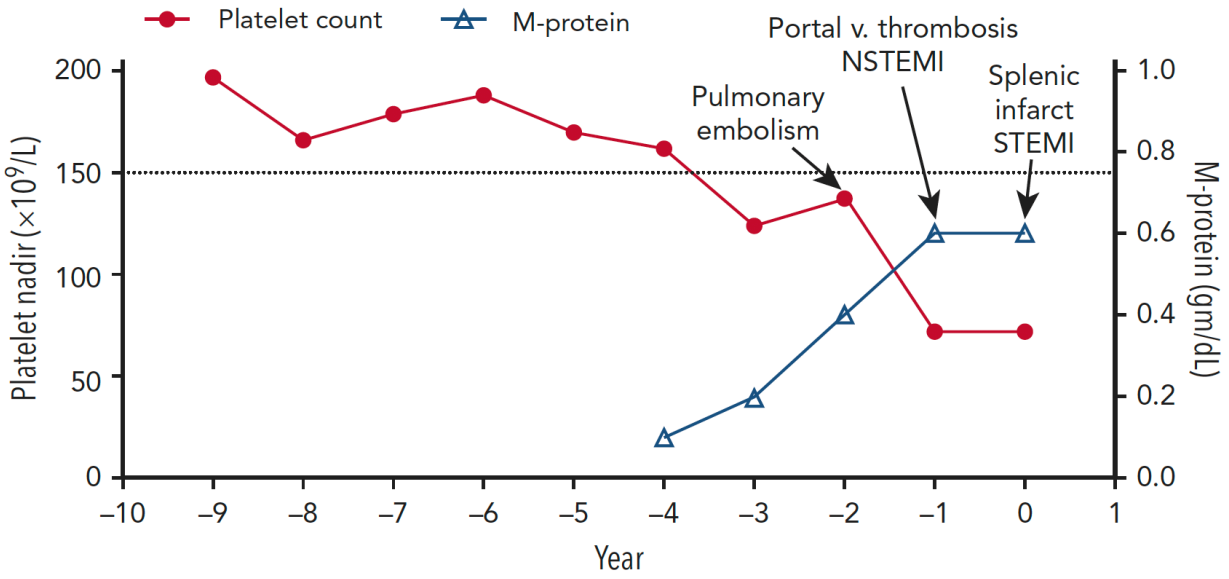


Monoclonal gammopathy of thrombotic/thrombocytopenic significance

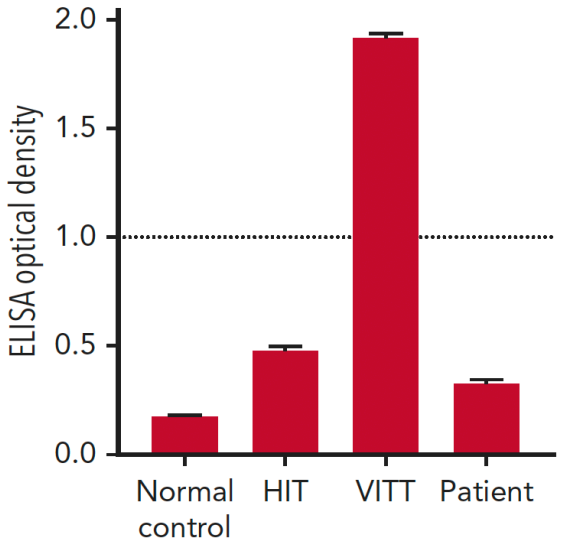
Adam J. Kanack,[1,*] Jordan K. Schaefer,[2,*] Meera Sridharan,[3,*] Noah P. Splinter,[1] Mindy C. Kohlhagen,[1] Bandana Singh,[1] Silvana B. De Lorenzo,[1] Emily E. Mauch,[1] Maen A. Hussein,[4] Marwan Shaikh,[5] Shaji Kumar,[3] Renren Wen,[6] Demin Wang,[6] David Murray,[1] and Anand Padmanabhan[1]

Blood 2023

64 year-old man with pulmonary emboli, portal vein thrombosis, non-ST elevation myocardial infarction, splenic infarction, and ST elevation myocardial infarction



HIT-Like Syndrome

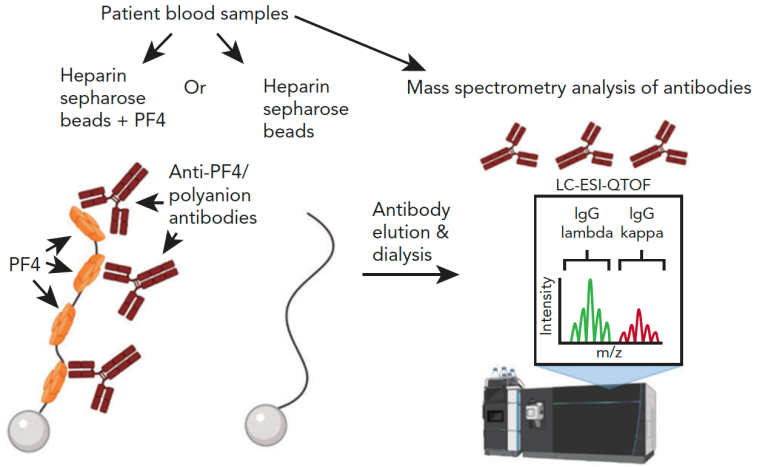


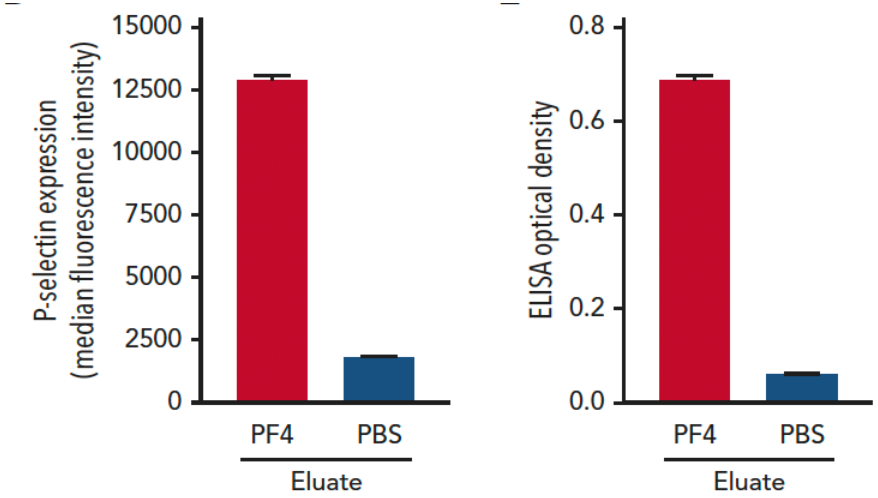
Faille D, Hurtado-Nedelec M, Ouedrani A, et al. Isolation of a monoclonal IgG kappa with functional autoantibody activity against platelet factor 4/heparin from a patient with a monoclonal gammopathy of undetermined significance and clinically overt heparin thrombocytopenia [abstract]. *Res Pract Thromb and Haemost.* 2017;1(suppl. 1):1355 (plus poster. Abstract PB 2360.

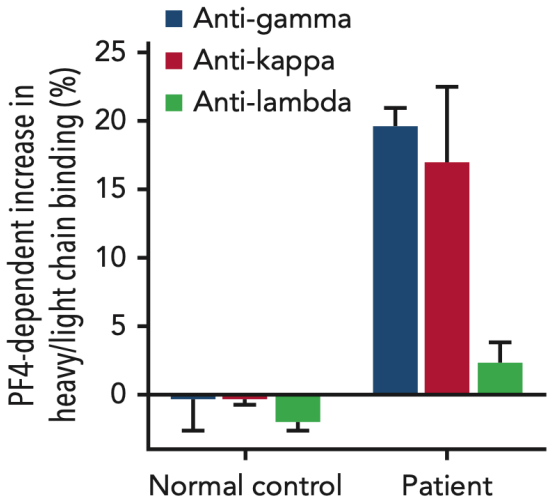
Monoclonal gammopathy of thrombotic/thrombocytopenic significance

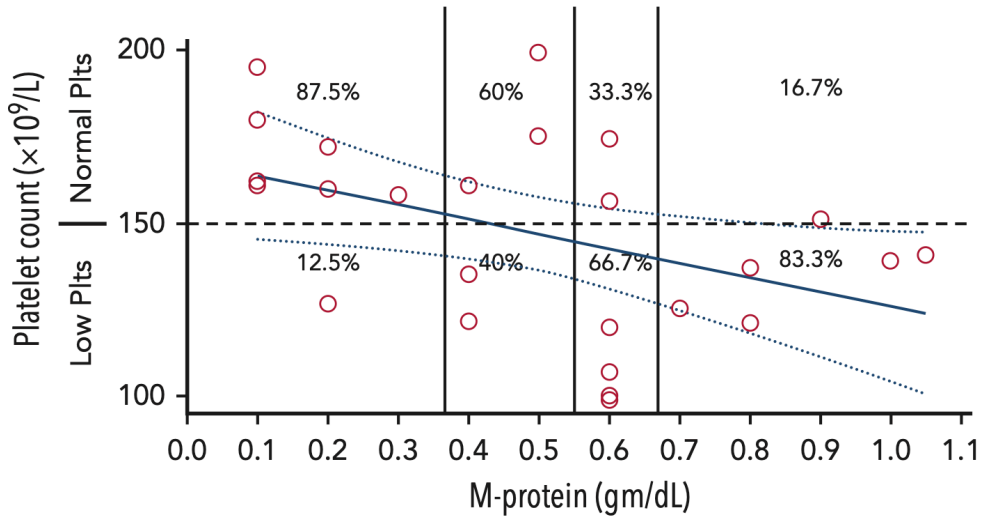
Blood 2023

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VITT-like Monoclonal Gammopathy of Thrombotic Significance

Wang JJ et al. N Engl J Med. 2025

Characteristic	VITT-like MGTS					Postviral VITT (N=5)
	Patient 1	Patient 2	Patient 3	Patient 4	Index Patient†	
Age at onset (yr)	60	46	35	47	79	Range, 5–58; one child
Sex	Male	Male	Male	Female	Female	Three female; two male
Duration of illness	4 yr	4 yr (died)	22 yr	5 yr	4 yr	Acute (weeks)
Initial platelet count (per mm³)	152,000	199,000	44,000	50,000	250,000	Not reported
Platelet count nadir (per mm³)	21,000	10,000 (at death)	23,000	30,000	81,000	Range, 10,000–38,000
Cerebral venous sinus thrombosis	No	Yes (fatal)	No	Yes	No	Yes in 3 patients
Splanchnic-vein, adrenal-vein, or renal-vein thrombosis	Yes (hepatic vein)	Yes (both adrenal veins)	Yes (mesenteric and splenic veins)	Yes (renal vein)	No	Yes in 1 patient
Deep-vein thrombosis	Yes	Yes	Yes	Yes	Yes	Yes in 2 patients
Superficial-vein thrombosis	No	Yes	No	Yes	No	Yes in 1 patient
Pulmonary embolism	Yes	No	Yes	Yes	Yes	Yes in 1 patient
Arterial thrombosis	Yes	No	Yes	No	Yes (arterial stroke)	Yes in 1 patient
Solid-phase PF4–polyanion ELISA‡	Positive (2.22 OD units)	Positive (2.29 OD units)	Positive (2.15 OD units)	Positive (2.30 OD units)	Positive (3.10 OD units)	Positive in all 5 patients
PF4–polyanion CLIA§	Negative	Negative	Negative	Negative	Negative	Negative in all 5 patients
Fluid-phase PF4 ELISA or PF4 CLIA¶	Positive fluid-phase ELISA (VITT-like)	Positive fluid-phase ELISA (VITT-like)	Positive CLIA (VITT-like)	Positive CLIA (VITT-like)	Positive CLIA (VITT-like)	Positive fluid-phase ELISA (VITT-like) in all 5 patients
Platelet-activation assay	Strongly positive SRA	Strongly positive SRA	Strongly positive PIPA	Strongly positive PIPA	Strongly positive PIPA	Strongly positive SRA in all 5 patients
M protein detected‖	Monoclonal IgGκ (0.29 g/dl)	Monoclonal IgGλ (<0.10 g/dl)	Monoclonal IgGλ (0.30 g/dl)	Monoclonal IgGλ (0.13 g/dl)	Monoclonal IgGκ (0.14 g/dl)	None
VITT-like anti-PF4 antibody identical to paraprotein	Yes	Yes	Yes	Yes	Yes	Not applicable

5 patients with **chronic** prothrombotic disorders featuring **anticoagulant-refractory thromboses** and intermittent **thrombocytopenia,** associated with **VITT-like antibodies**

Low levels of M proteins (median = 0.14 g/dl)

In each patient, the M protein was the VITT-like antibody

VITT-like Monoclonal Gammopathy of Thrombotic Significance

Wang JJ et al. N Engl J Med. 2025

The **antibody clonotype profiles**

A Anti-PF4 Antibody Fingerprints

	Immunoglobulin light chain		Immunoglobulin heavy chain		Clonotype profile
	IGLV	LCDR3	IGHV	HCDR3	
Postviral VITT (N=5)	IGLV3-21*02	QXWDXXXDHXXF		XXXXXXXXEDXFDXW	Stereotype
VITT-like MGTS, index patient	IGKV1-5*01	QQYNNYPYTF	IGHV3-21*01	ARDQDVVLVPAASSGYDAFDVW	Individual
VITT-like MGTS, Patient 1	IGKV5-2*01	LQHDNFPLTF	IGHV3-30*03	ARDLSRYGGDFGNYVGMDVW	Individual
VITT-like MGTS, Patient 2	IGLV3-21*02	QVWDRSSDHWVF	IGHV3-15*06	TADFSNVWDSGDSWVDPW	Individual
VITT-like MGTS, Patient 3	IGLV2-23*03	CSYAVSSTSAVF	IGHV1-24*01	ATVDGDSVYHFDHW	Individual
VITT-like MGTS, Patient 4	IGLV1-47*02	AAWDDSLSGRVF	IGHV3-72*01	AKDADWNYEYDVW	Individual

Anti-PF4 mediated thrombocytopenia and thrombosis associated with acute cytomegalovirus infection displays both HIT-like and VITT-like characteristics

37-year-old female with **fever and abdominal pain.**

Her blood tests showed **thrombocytopenia, a low fibrinogen and a very high D-dimer level.**

Imaging revealed a **portal vein thrombosis.**

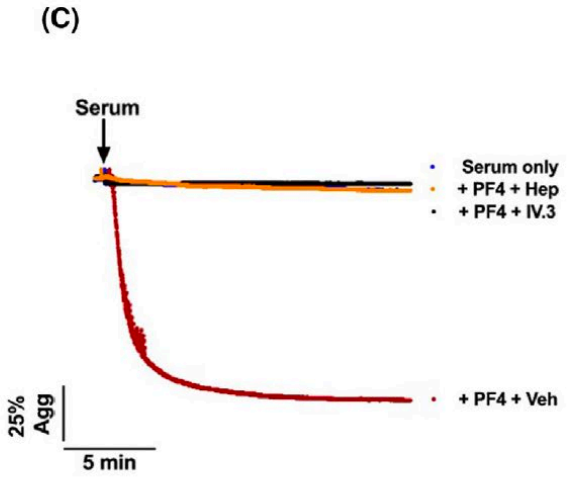
PF4-specific ELISA testing strongly **positive** (>3.0 OD) with 98% neutralization with 0.5 U/mL heparin.

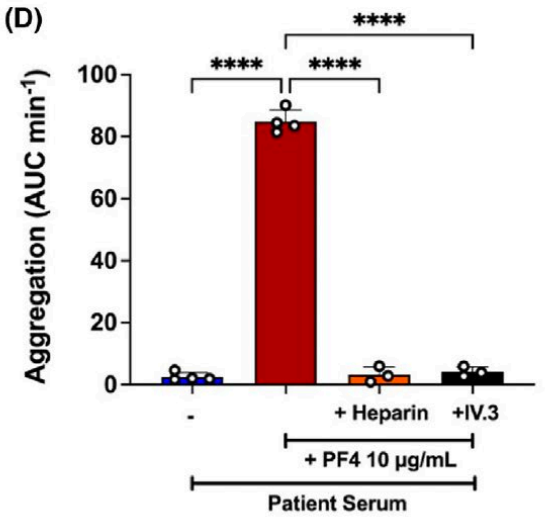
Viral analyses confirmed the diagnosis of **acute cytomegalovirus infection**

SPE revealed a **monoclonal IgGλ band of <0.1 g/dL.** Clonotyping of this paraprotein revealed it to be the **same IgGλ anti-PF4 antibody**

(B)

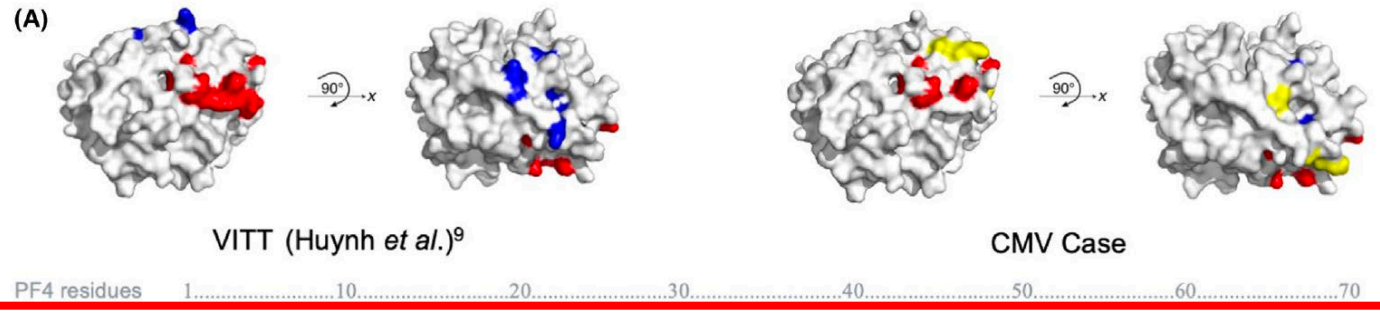
		Serum					
	Heparin (U/mL)	-	0.3	100	0.1	-	-
	PF4 (10 µg/mL)	-	-	-		+	+
Assay	IV.3 (10 µg/mL)	-	-	-	+	-	+
SRA		100 %	100 %	0 %	1 %	100%	13 %



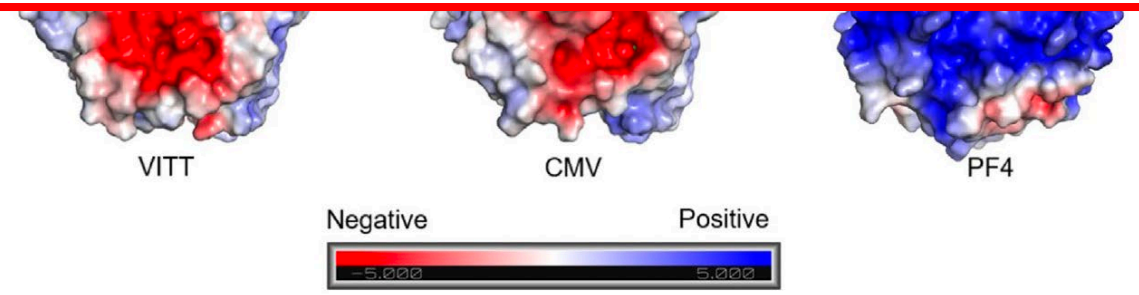


Nicolson PLR et al. Br J Haematol. 2025;206(6):1737-1742.

Anti-PF4 mediated thrombocytopenia and thrombosis associated with acute cytomegalovirus infection displays both HIT-like and VITT-like characteristics



« Since it is not always possible
to classify all patients into separate HIT, VITT and various subtype diagnostic categories ,
the authors proposed the name of
PF4-associated immune thrombocytopenia and thrombosis (PITT) as an overarching term. »



Nicolson PLR et al. Br J Haematol. 2025;206(6):1737-1742.

Heterogeneity of PF4-specific antibodies

Important practical consequences

1/ To clinically identify patients with VITT-like or HIT-like disorders

2/ To biologicallydistinguish VITT antibodies from HIT antibodies

3/ To treat efficiently severe disorders due to anti-PF4 antibodies

When to suspect « VITT-like » Syndromes ?

- **Thrombocytopenia and severe thrombosis**
  in patients **not exposed to heparin or an adenovirus vaccine**
  AFTER an infection within the previous 15 days

- **A monoclonal anti-PF4 antibody-related disease has to be suspected when:**

1. A **thrombocytopenia chronic**/progressive or intermittent is present (with exacerbations in platelet count decline often occurring in association with thrombosis)
2. A **wide spectrum of thrombotic events** is observed, with atypical localisation (particularly cerebral venous thrombosis) and recurrence while the patient is receiving therapeutic-dose anticoagulation

Diagnosis of VITT-like Sd due to a monoclonal paraprotein

The M-protein levels are most often low

A patient may be identified as having VITT-like MGTS even though a paraprotein is not detected by standard SPEP/IFE techniques

The lower limit of paraprotein detectability (~0.20 g/L) is considerably greater than the concentration of VITT-like monoclonal antibodies that can cause platelet activation under test conditions (15–60 µg/mL [0.015–0.060 g/L]).

➡️ In such a (theoretical) patient, **despite an M-protein not being readily identifiable (by SPEP/IFE), the patient will tested positive by PF4/polyanion ELISA and a PF4-enhanced platelet activation assay**.

Warkentin, Int J Lab Haematol, 2026

J Thromb Haemost, 2026

Platelet factor 4 antibody persistence and long-term pathogenicity in vaccine-induced immune thrombotic thrombocytopenia

Adam Kanack[1] | Emily Mauch[1] | Guillaume Roberge[2] | Noah Splinter[1] | Krishna Gundabolu[3] | Geoffrey D. Wool[4] | Gemlyn George[5] | Mouhamed Yazan Abou-Ismail[6] | Kristi J. Smock[7] | David L. Green[8] | Jonathan Coker[1] | Mindy C. Kohlhagen[1] | David L. Murray[1] | Anand Padmanabhan[1]

MGUS not detectable by conventional biochemical methods

Monoclonal gammopathy of thrombotic significance in a nutshell

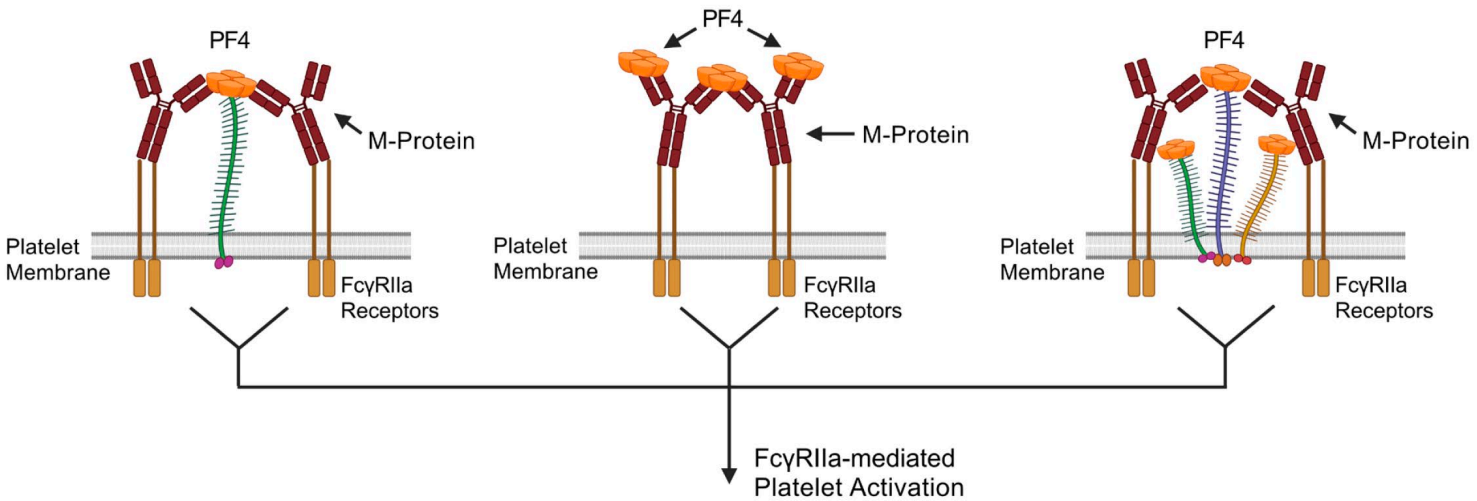
Brit J Haematol, 2026

Adam J. Kanack | Emily E. Mauch | David L. Murray | Anand Padmanabhan

Monoclonal Gammopathy of Thrombotic Significance (MGTS)

HIT-like MGTS **(B)** VITT-like MGTS **(C)** Non-HIT/VITT-like MGTS

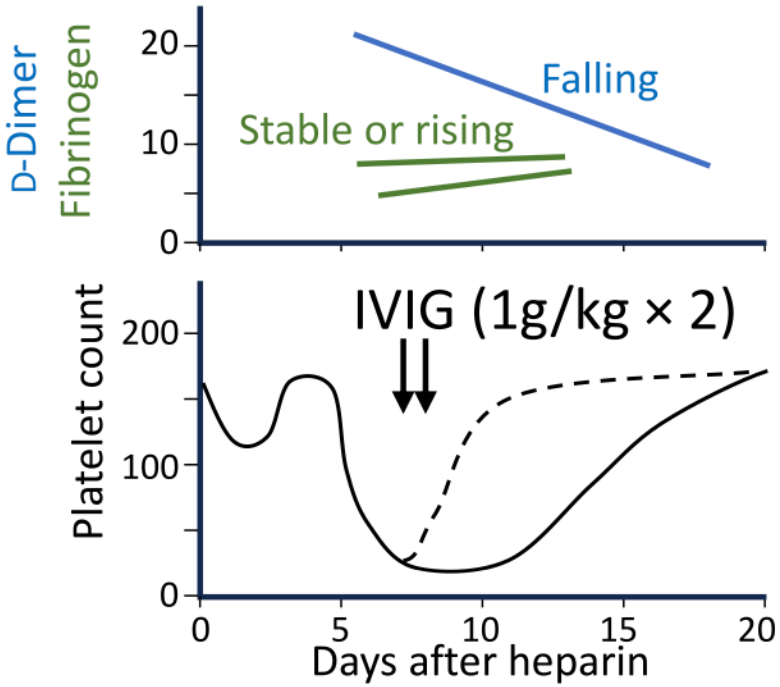
MGTS subtype			
Assay	**HIT-like**	**VITT-like**	**Non-HIT/VITT-like**
Solid-phase HIT ELISA	+	+	–
Solid-phase VITT ELISA[a]	–	+	–
Automated PF4-PVS HIT assays (LIA/CLIA)	+	–	–
Serotonin release assay (SRA)	+	–/+	–
PF4-dependent P-selectin expression assay (PEA)/ PF4-SRA	+	+	+



Treatment of immunothrombotic disorders due to anti-PF4 antibodies & different than typical HIT:

Auto-immune HIT, VITT, VITT-like syndromes

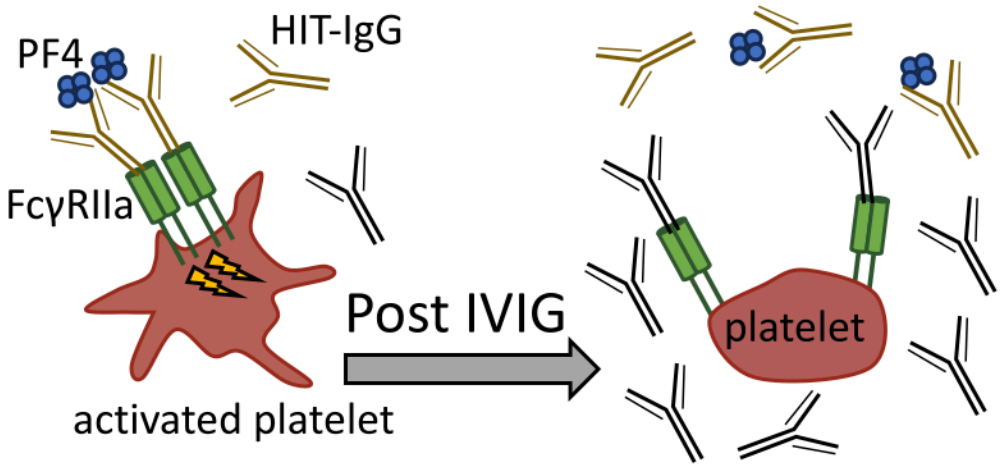
Usefulness of IvIg for the treatment of disorders induced by anti-PF4 antibodies (atypical HIT, VITT…)



Low platelet counts signify heparin-independent platelet-activating properties (inhibitable by IVIG)

Daily fibrinogen (stable, rising) and D-dimer (falling) values help assess if HIT hypercoagulability is "cooling off"

Plasma IgG (concentration-dependent) inhibits PF4/IgG immune complexes from activating platelets via FcγIIa receptors[9-11]



- *Warkentin TE.. Res Pract Thromb Haemost. 2023*

VITT-like Monoclonal Gammopathy of Thrombotic Significance

Wang JJ et al. N Engl J Med. 2025 Mar 6;392(10):995-1005.

