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Spontaneous post-orthopedic HIT-like syndrome: a case report and literature review with diagnostic / therapeutic recommendations for a rare life-threatening complication

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BACKGROUND, AIM AND METHODS

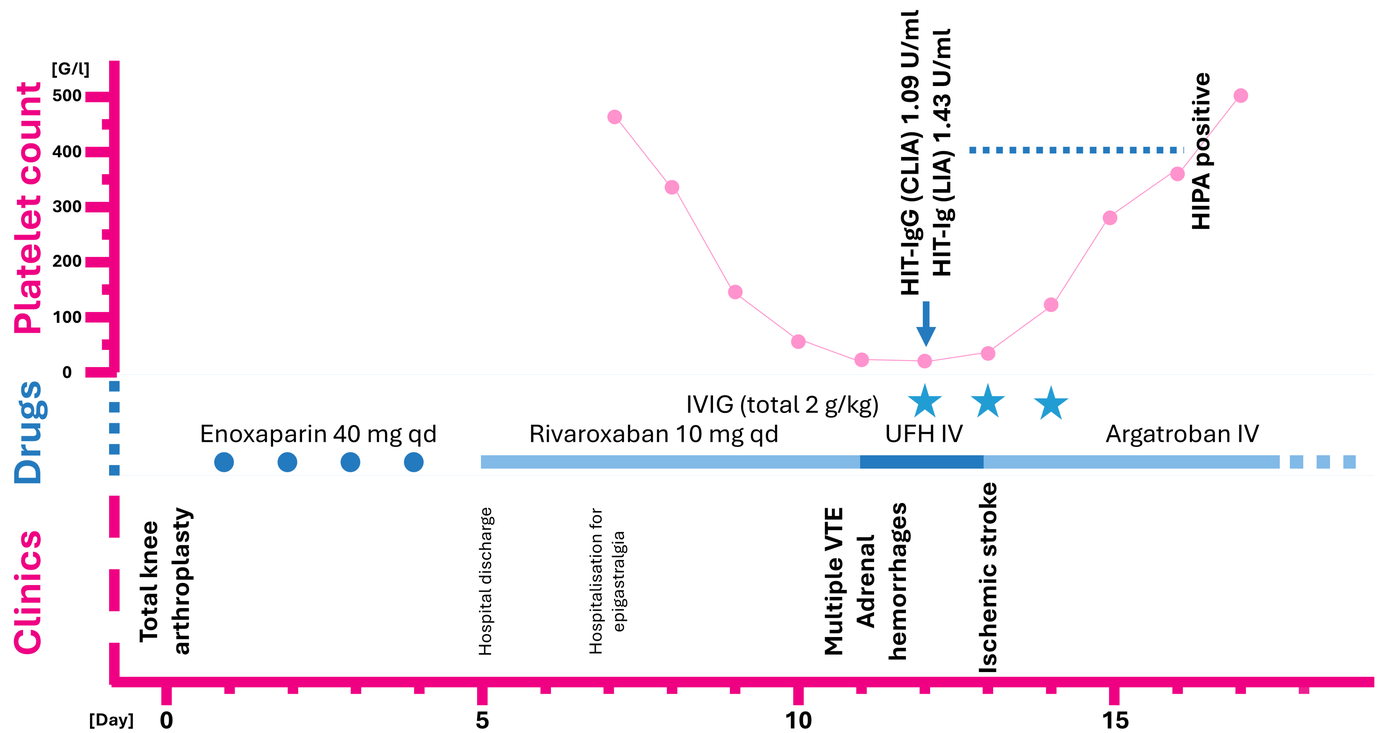
- Autoimmune heparin-induced thrombocytopenia (aHIT) is a subtype of HIT due to both heparin-dependent and heparin-independent anti-PF4 antibodies that activate platelets leading to thrombocytopenia and thrombo-embolic complications
- aHIT regroups several subtypes, including spontaneous heparin-induced thrombocytopenia-like syndrome (spHIT) and delayed-onset HIT (doHIT)
- spHIT is a rare but severe thromboembolic complication typically occurring after orthopedic surgery, particularly total knee arthroplasty (TKA), without exposure to heparin
- doHIT is another type of aHIT manifesting after cessation of heparin treatment
- spHIT can be difficult to distinguish from delayed-onset HIT (doHIT)
- Given the limited number of reported cases of spHIT, guidelines for diagnosis and management are lacking
- We aim to describe a new case of spHIT after TKA and suggest diagnostic and therapeutic approaches
- We report an unpublished case followed at the Lausanne University Hospital and a review of published spHIT-cases (n=22)

SPONTANEOUS HIT-LIKE SYNDROME TAKE-HOME MESSAGES

- **CLINICS**
  - **POST-TOTAL KNEE ARTHOPLASTY**
  - **SEVERE VENOUS AND ARTERIAL THROMBO-EMBOLIC MANIFESTATIONS**
  - **HIGH RATE OF ADRENAL INFARCTIONS OR HEMORRHAGES**
- **DIAGNOSTICS**
  - **4T SCORE CONSIDERING THE SURGERY DAY AS DAY 0**
  - **IMMUNOASSAYS**
  - **CONFIRMATION WITH FUNCTIONAL TESTS**
- **THERAPEUTICS**
  - **EARLY ADMINISTRATION OF IVIG**
  - **NON-HEPARIN ANTICOAGULATION**

RESULTS AND METHODS

- Clinics
  - SpHIT is a prothrombotic condition that is likely underdiagnosed, as recognized only after thromboembolic complications
  - Thrombotic manifestations are typically severe to very severe
  - In particular, adrenal infarctions or hemorrhages (secondary to adrenal vein thrombosis) should prompt consideration of spHIT in post-orthopedic surgery patients
  - The context, the absence of heparin exposure and the severity of the thrombo-embolic manifestations help to distinguish spHIT from other aHIT
- Our case
  - Due to post-surgery exposition to low-molecular weight heparin, delay-onset HIT can be considered
  - However, based on the brief exposition, the post-TKA context, and the severity of the thrombo-embolic manifestations, spHIT is very probable
- Diagnostics
  - Considering the surgery day as day 0, the 4T score appears adequate to assess pretest probability, with high scores reported in all cases.
- Therapy
  - Prompt initiation of non-heparin anticoagulation is warranted.
  - Early administration of IVIG is key for a successful treatment, given the frequent argatroban resistance.



Presentation of an unpublished case. Platelet count in G/l. CLIA, chemiluminscence immunoassay; HIPA, heparin-induced platelet aggregation assay; IV, intravenous; IVIG, intravenous immunoglobulins; LIA, latex immunoassay; PE, pulmonary embolism; qd, once a day; UFH, unfractionnated heparin; VTE, venous thrombo-embolic events.

Study	year	Age [years]	Surgery	4T score	Thrombo-embolic events	Acute treatment	Further treatment	Outcome
SYNTHESIS	**NA**	**NA**	**TOTAL KNEE ARTHROPLASTY**	**≥5**	**100%, OFTEN SEVERE MANIFESTATIONS 52% ADRENAL HEMORRHAGES**	**ALTERNATIVE ANTICOAGULATION IVIG**	**AVK/DOAC VARIABLE DURATION**	**HIGH RATE OF ARGATROBAN RESISTANCE MORTALITY 4.3%**
Illustrative case	2025	57	Total knee arthroplasty	7	Renal vein, hepatic vein thromboses, PE, bilateral adrenal hemorrhage; CVI under heparin	Argatroban IVIG (total 2 g/kg on three days)	Acenocoumarol for three months	Platelet count recovery under argatroban and IVIG
Olevsky and Rosove	2021	57	Total knee arthroplasty	7	Acute segmental PE, acute left poplietal DVT	Therapeutic argatroban	Rivaroxaban for six months	Platelet count recovery and D-dimers decrease
Olevsky and Rosove	2021	70	Total knee arthroplasty	6	Femoral artery thrombosis, with rethrombosis, amputation under UFH; PE under UFH	Therapeutic argatroban	Rivaroxaban for an unclear duration	Platelet count recovery over two weeks
Warkentin and Greinacher	2021	70	Total knee arthroplasty	7	Popliteal DVT; iliac artery thrombosis; Rethrombosis (DVT, PE, arterial) at day 36/38, amputation	Therapeutic argatroban with thromboses, rivaroxaban 2x 15 mg, IVIG	Rivaroxaban 2x 15 mg	Resistance to argatroban, partial platelet count recovery under rivaroxaban and IVIG
Saengbon et al.	2021	68	Bilateral total knee arthroplasty	6	Lower extremity arterial oclusion, progression under UFH; adrenal hemorrhage	Fondaparinux IVIG (1 g/kg on two following days)	Apixaban for six months	Platelet count recovery after fondaparinux and IVIG
Hwang et al.	2020	56	Total knee arthroplasty	7	Cerebral venous sinus thrombosis, DVT of the left internal jugular vein	Bivalirudin IVIG (1 g/kg on two following days)	Long-term warfarin	Platelet count recovery
Swarup et al.	2020	33	Left femoral and neck currettage, bone grafting	8	PE in main and descending pulmonary arteries, extensive proximal and distal DVT	Therapeutic argatroban	Warfarinf or two years	Platelet count recovery in one week
Hornick and Ayafor	2020	51	Bilateral total knee arthroplasty	6	Bilateral distal main PE, bilateral femoral and popliteal DVT	Rivaroxaban	Rivaroxaban for six months	Platelet count recovery at one month
VanderVeer et al.	2019	68	Total knee arthroplasty	8	Bilateral adrenal infarction	Prophylactic rivaroxaban until day 28	NA	Platelet count recovery
Alidoost et al.	2019	68	Total knee arthroplasty	7	Bilateral adrenal hemorrhage; after IVC filter placement: DVT from the IVC to the lower extremity	Therapeutic argatroban	Warfarin for an unclear duration	Platelet count recovery
Mohanty et al.	2019	52	Total knee arthroplasty	8	Ischemic colitis / mesenteric ischemia	Therapeutic argatroban, fondaparinux IVIG (1 g/kg on two following days)	Fondaparinux for an unclear duration	Resistance to argatroban and fondaparinux, platelet count recovery after IVIG
Poudel et al.	2017	53	Total knee arthroplasty	6	Acute PE	Fondaparinux, argatroban with new DVT	Rivaroxaban	Resistance to fondaparinux/argatroban, platelet count recovery under rivaroxaban
Baker and Lim	2017	72	Total knee arthroplasty	7	Bilateral PE, left cephalic, left common femoral, left popliteal, right posterior tibial vein DVT	Therapeutic argatroban, IVC filter placement, platelet transfusion	Apixaban for three months	Platelet count recovery at day 28
Elshoury et al.	2015	48	Total knee arthroplasty	8	Bilateral adrenal hemorrhage; bilateral PE	Therapeutic argatroban with recurrent PE, IVC filter placement	Warfarin	Resistance to argatroban, platelet count recovery
Warkentin et al.	2015	71	Total knee arthroplasty	7	Bilateral adrenal hemorrhage; PE, infeiror vena cava and popliteal DVT	Therapeutic argatroban	Fondaparinux for three months	Platelet count recovery
Warkentin et al.	2014	54	Shoulder hemiarthroplasty	7	Lower-extremity DVT; acute CVI of the left posterior inferior cerbellary artery territory	Therapeutic argatroban	Fondaparinux for three months	Platelet count recovery
Ketha et al. (4 cases)	2013	60, 65, 71, 61	Total knee arthroplasty	5, 5, 6, 6	Adrenal hemorrhage	NR	NR	NR
Mallik et al.	2011	60	Bilateral total knee arthroplasty	7	Left popliteal DVT, bilateral lower extremity DVT under argatroban	Therapeutic argatroban, IVIG (1 g/kg on two following days) after rethrombosis	Warfarin for 10 months	Resistance to argatroban, platelet count recovery after IVIG
Pruthi et al.	2008	61	Total knee arthroplasty	8	Bilateral adrenal hemorrhage; saphenous SVT, non-occlusive popliteal and femoral DVT	IVC placement, argatroban with PE and progression of DVT, tepirudin	Warfarin for an unclear duration	Platelet count recovery
Jay and Warkentin	2008	69	Total knee arthroplasty	8	Lower extremity DVT; digital infarcts; bilateral adrenal hemorrhage, DIC, death	Danaparoid	NA	Platelet count recovery, death from complications of anoxic brain damage

Review of the published post-orthopedic spHIT-cases. AVK, antivitamin K; DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulants; DVP, deep vein thrombosis; IVC, inferior vena cava; IVIG, intravenous immunoglobulins; NA, not applicable; NR, not reported; PE, pulmonary embolism; UFH, unfractionnated heparin.