Trombocitopenia da eparina

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Irene, 32 anni

- 51 Kg x 165 cm
- Dal 1990 diagnosi di LES + anticoagulante lupico, trattata con immunosoppressori
- Nota eterozigosi per mutazione della protrombina G20210A
- Giugno 2000: TVP poplitea sin “spontanea” + EP, trattata con LMWH, da allora TAO
- Riferisce instabilità valori di INR e gravi menorragie

L’evoluzione

- Marzo 2008: recidiva TVP + EP (stessa sede)

✓Trattata con LMWH, prosegue TAO

- Agosto 2008: trombosi venosa cerebrale

✓Sospesa TAO, terapia con LMWH (enoxaparina 1 mg/Kg x 2/die)

- Agosto 2008, venerdì: da 2 giorni ripresa di sintomatologia cefalgica ed episodi di vomito

Una terapia “al buio”

- Agosto 2008, venerdì pomeriggio: suggerita rivalutazione urgente di laboratorio + neurologica e angioRMN
- Piastrinopenia (-50% circa rispetto ai valori abituali della paziente); in attesa altri accertamenti

✓Sostituzione di LMWH con fondaparinux (Arixtra, 5.0 mg/die)

L’evoluzione

- Sabato-domenica: aumento del numero delle piastrine e regressione dei sintomi (cefalea e vomito)
- Lunedì pomeriggio: elevata positività anticorpi anti PF4; normalizzazione del numero delle piastrine
- Stabilità del quadro angio-RMN
- Martedì-giovedì: normalizzazione del quadro clinico e dimissione

ESAMI DI TROMBOFILIA
DATA: 25/10/2010
COGNOME NOME: ------- **IRENE**

			Valori Normali
Antitrombina			
Funzionale	103		(82-112%)
Proteina C			
Funzionale Amidolitico	84		(67-119%)
Proteina S			
Antigene della libera (PEG)	107		(M 60-158% - F 49-124%)
PS funzionale (ProS)	94		(F 62-122 - M 78-138)
Resistenza alla proteina C attivata	0,64		(ratio 0.74-1.30)
Mutazione G1691A fattore V (Leiden)	assente		(Assente)
Mutazione G20210A protrombina eterozigote: 20210 AG			(Assente)
Omocisteina (FPIA)			
Basale	7,5		(F:17.2 µmol/L- M:22.5 µmol/L)
Dopo carico metionina (a 4h)	27,2		(F:44.3 µmol/L- M:52.2 µmol/L)
Incremento	19,7		(F:28.4 µmol/L- M:28.9 µmol/L)
Vitamina B12	319		(191-663 pmol/l)
Acido folico	7,1		(3.1-17.5 nmol/L)
	Ratio	Secondi	
PT	1,20	13,1	(ratio 0.94-1.15)
PT mix 50/50	1,13	11,9	(ratio 0.94-1.15)
	Ratio	Secondi	
PTT	**2,50**	78,4	(ratio 0.84-1.14)
PTT mix 50/50	**1,80**	55,7	(ratio 0.84-1.14)
Fibrinogeno	238		(200-400 mg/dl)
Fattore VIII	75		(50-150%)
Test per ricerca anticorpi antifosfolipidi			
SCT screen	**2,98**		(<1.22)
SCT confirm	**1,42**		
SCT screen/confirm ratio	**2,11**		(<1.27)
LAC screen	**1,55**		(<1.14)
LAC confirm	**1,06**		
LAC screen/confirm ratio	**1,46**		(<1.15)
Anticardiolipina IgG (ELISA)	1		(<20 GRL= assente)
Anticardiolipina IgM (ELISA)	7		(<20 MPL= assente)
Anticorpi anti beta2-GP1 IgG	5		(<5 U/ml)
Anticorpi anti beta2-GP1 IgM	2		(<5 U/ml)

Intravenous Immune Globulin to Prevent Heparin-Induced Thrombocytopenia

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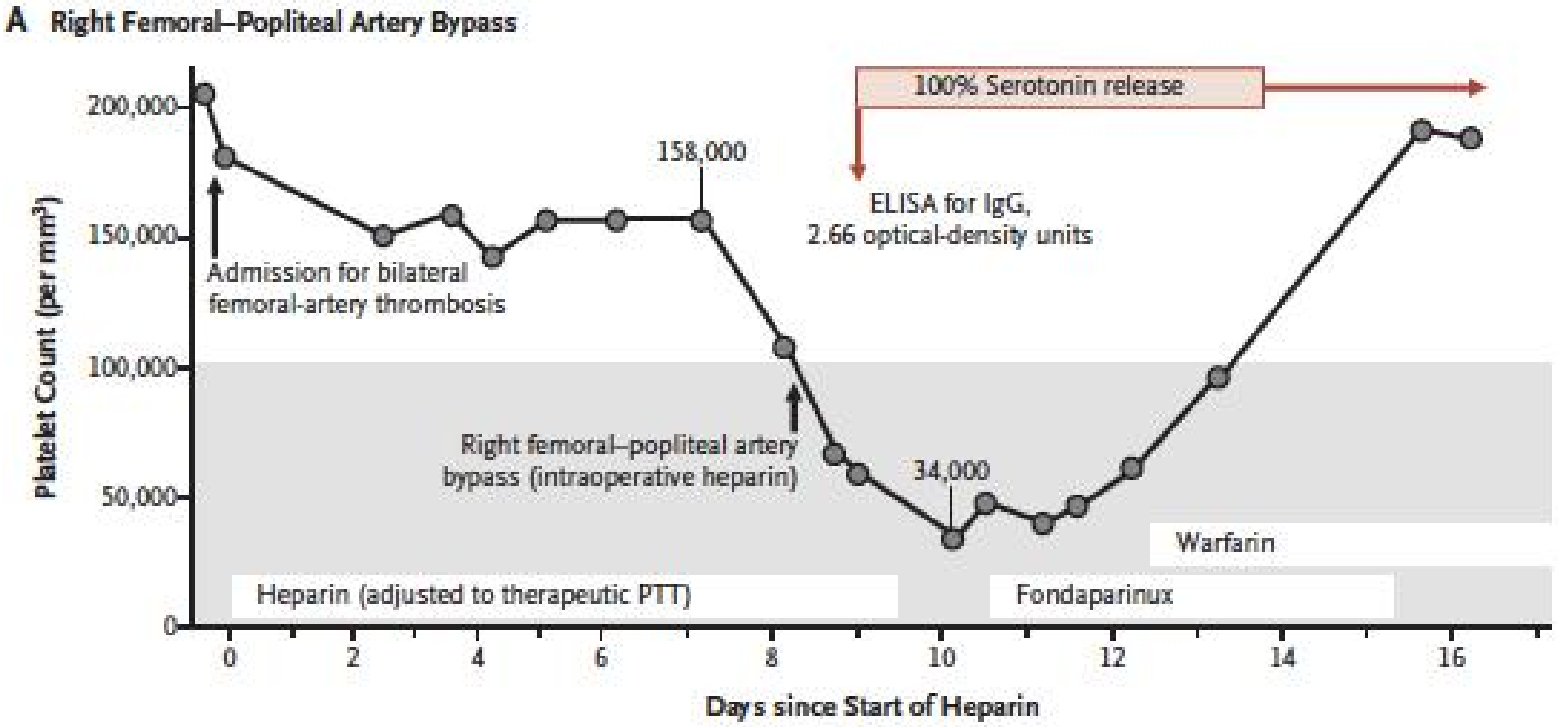
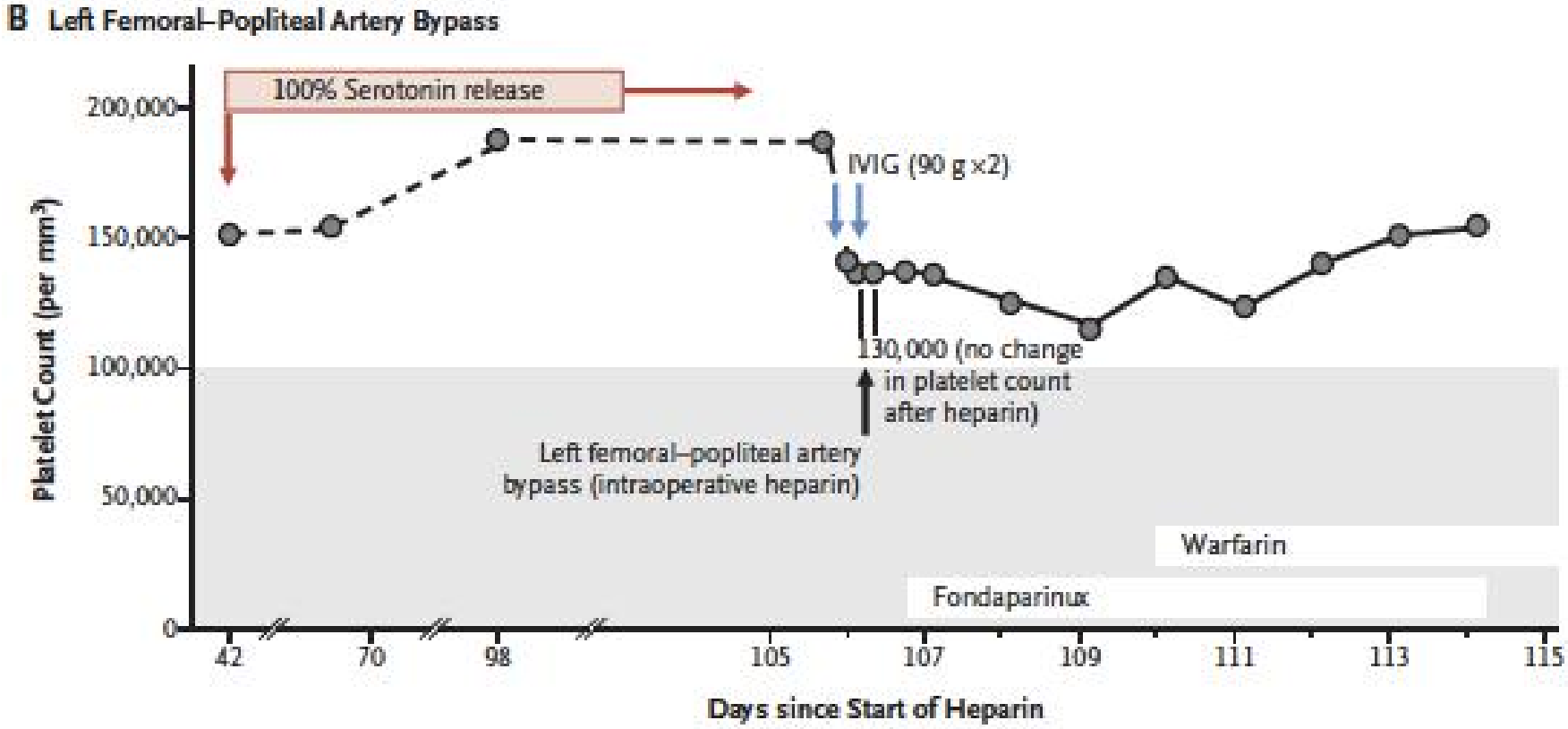
Case report

- HIT developed in a 59-year-old man while he was receiving heparin for symptomatic atherothrombosis involving both superficial femoral arteries
- Vascular surgery in the left femoral artery was postponed pending disappearance of the platelet activating antibodies
- After 13 weeks, progressive ischemic necrosis of the distal left lower limb occurred, and urgent revascularization was recommended
- However, the patient's serum still showed 100% heparin dependent serotonin release


A Right Femoral–Popliteal Artery Bypass
100% Serotonin release
ELISA for IgG,
2.66 optical-density units
158,000
Admission for bilateral
femoral-artery thrombosis
Right femoral–popliteal artery
bypass (intraoperative heparin)
34,000
Warfarin
Heparin (adjusted to therapeutic PTT)
Fondaparinux
Platelet Count (per mm³)
200,000
150,000
100,000
50,000
0
0
2
4
6
8
10
12
14
16
Days since Start of Heparin

Treatment

- The patient received IVIG, at a dose of 90 g, beginning 9 hours before surgery, and a second 90-g dose given during surgery
- He received 7000 units of heparin during surgery; the platelet count, which was 130,000 per cubic millimeter immediately before the administration of heparin, was unchanged 2 hours after the heparin bolus
- The surgery was successful, without thrombotic complications
- The platelet-inhibitory effects of IVIG were transient, with return to a strongly positive serotonin-release assay within 1 week

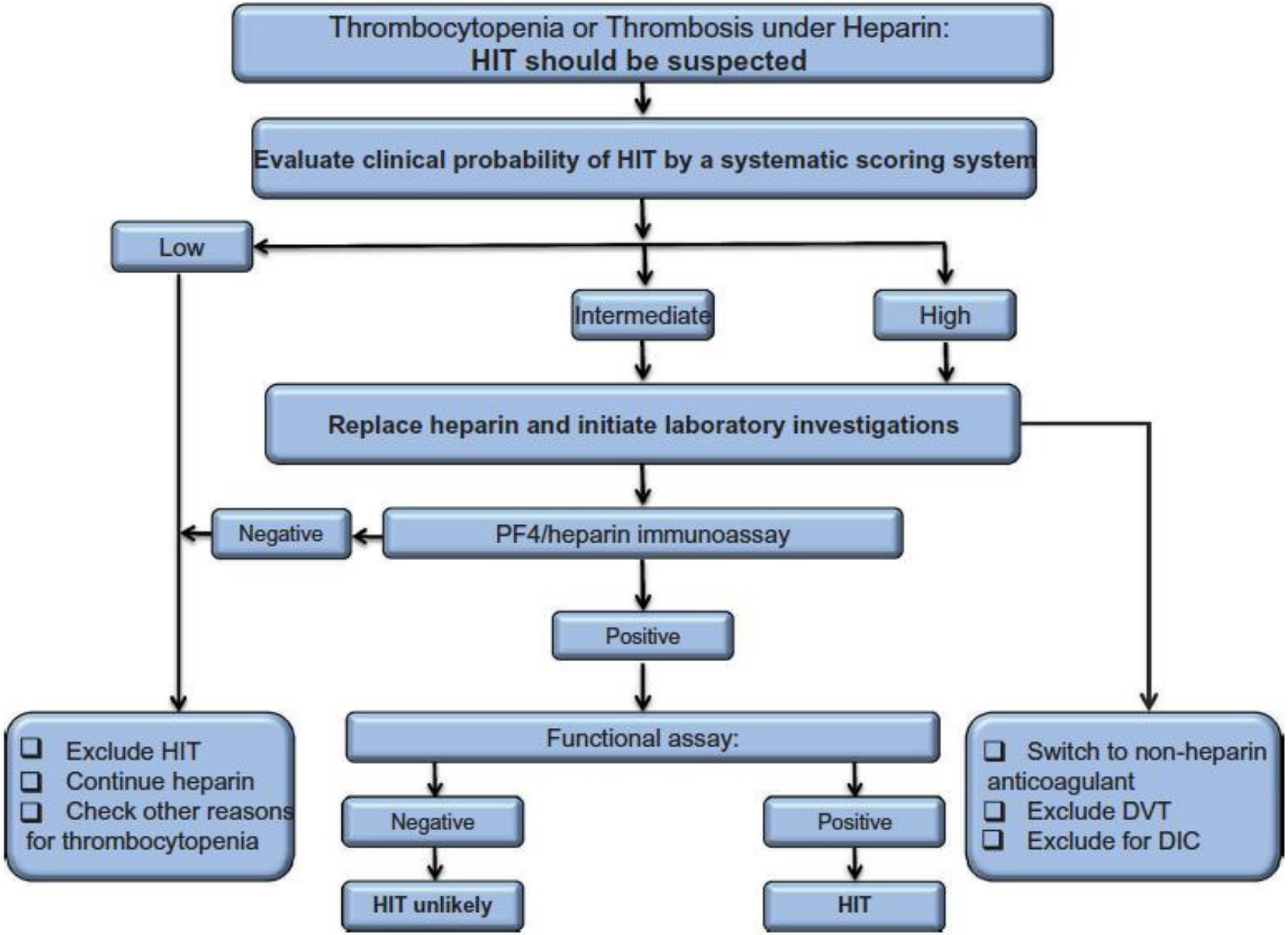

B Left Femoral–Popliteal Artery Bypass
100% Serotonin release
IVIG (90 g ×2)
130,000 (no change in platelet count after heparin)
Left femoral–popliteal artery bypass (intraoperative heparin)
Warfarin
Fondaparinux
Platelet Count (per mm³)
200,000
150,000
100,000
50,000
0
42
70
98
105
107
109
111
113
115
Days since Start of Heparin

Comments

- This finding offers a potential new approach for treating patients with recent HIT and residual platelet-activating antibodies who require urgent surgery in which heparin is used

Laboratory diagnosis

- **Functional assays**: high specificity (>95%) and PPV (89% to 100%) but low sensitivity (56 to 100%)
- **Immunoassays**: high sensitivity (99%) but low specificity (30% to 70%), increased through detection of IgG antibodies and quantification of OD and/or titers


Thrombocytopenia or Thrombosis under Heparin:
HIT should be suspected
Evaluate clinical probability of HIT by a systematic scoring system
Low
Intermediate
High
Replace heparin and initiate laboratory investigations
Negative
PF4/heparin immunoassay
Positive
Exclude HIT
Continue heparin
Check other reasons for thrombocytopenia
Functional assay:
Negative
HIT unlikely
Positive
HIT
Switch to non-heparin anticoagulant
Exclude DVT
Exclude for DIC

Treatment

- Starts at time of disease suspicion
- Discontinuation of all sources of heparin
- Avoid, delay or reverse VKA
- Therapeutic dose anticoagulation for at least 4 weeks in isolated HIT and 3 months in patients with thrombosis
- Selection of a parenteral agent is largely based on drug availability and patient co-morbidities (renal or hepatic dysfunction)

Drugs

- Argatroban: synthetic reversible inhibitor of thrombin, is approved for treatment of HIT based on 2multicenter trials comparing argatroban with historical controls
- Danaparoid: mixture of naturally occurring GAGs (heparan sulfate, dermatan, and chondroitin) sulfate. Approved in Europe, Canada…
- Bivalirudin: synthetic thrombin inhibitor cleared by plasma proteases and partially by renal excretion. Approved in USA for percutaneous cardiac intervention and who have HIT or at risk for developing HIT
- Fondaparinux
- DOACs

Take-home messages

- Evitare/limitare l'uso «cosmetico» di eparina
- Sospettare sempre una HIT in caso di recidiva tromboembolica in trattamento (anche in assenza di piastrinopenia)
- Se i test non sono rapidamente disponibili, sospendere eparina e sostituirla
- Nella scelta della terapia alternativa all'eparina, considerare fondaparinux e DOACs
- Documentare in cartella clinica le motivazioni delle scelte diagnostiche e terapeutiche: condividerle con colleghi e paziente