EUROPEAN HEMATOLOGY ASSOCIATION

EHA-TSH Haematology Tutorial on Immune Hematological Disorders

APS-Clinical Case

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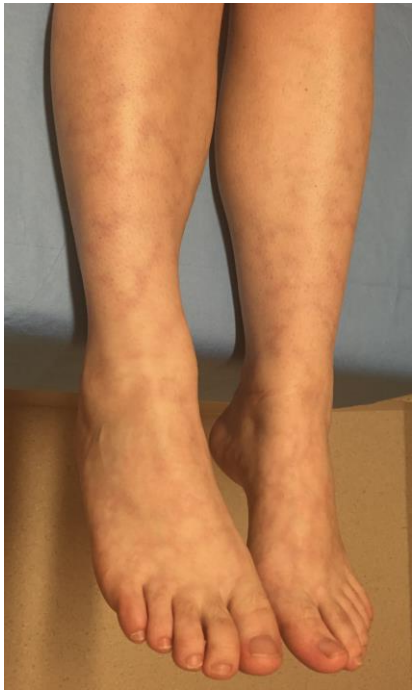
Clinical history

- A 24-year-old female patient was scheduled for operation due to nasal septum deviation
- She was referred to the Haematology Department because of the prolonged aPTT test in the pre-operative analysis
- She had no history of bleeding
- She had a tooth extraction 6 months ago with no excessive bleeding
- There was no family history of bleeding

A 24-year-old female patient with prolonged aPTT

- Physical examination was normal **except for livedo reticularis**
- 165 cm, 59 kg, BMI 21.7
- She was not using any medication or supplements
- She smokes 4-5 cigarettes per day and occasionally drinks alcohol



A 24-year-old female patient with prolonged PTT

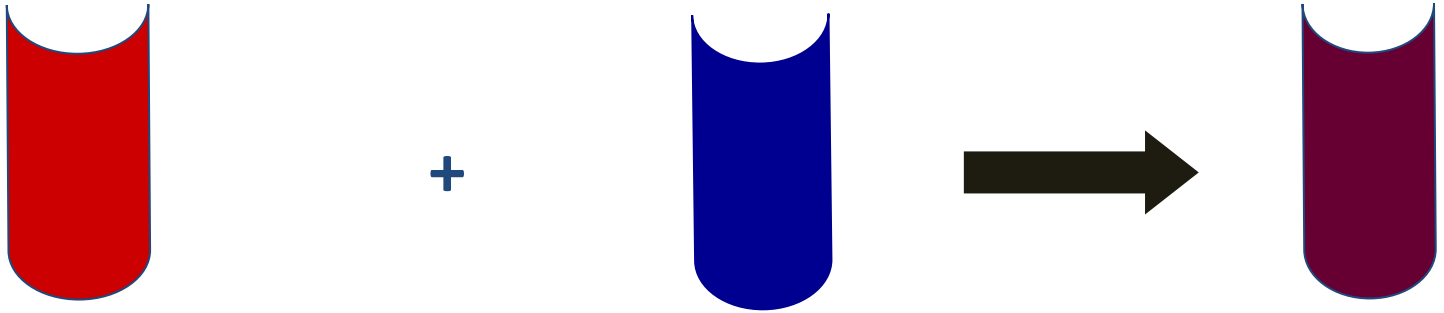
- **Biochemical analysis:** ESR, CRP, ALT, AST, LDH, creatinine were all in normal limits
- **FBC was normal:** Hb 137 g/l, WBC 6.45 x 10^9/l, Neutrophils 4.42 x 10^9/l, Platelet count 231 x 10^9/l
- **Coagulation tests:** PT 12.2 sec (N: 12-16 sec), INR: 1, ***PTT 72 sec (N: 32-39 sec),*** Fibrinogen 2.8 g/l (N: 1.5-4 g/l)

Isolated PTT Prolongation: Causes

- Factor VIII, FIX, FXI, FXII deficiencies or inhibitors
- Lupus anticoagulant
- Anticoagulant therapy

Mixing Test

In a patient with a specific factor deficiency, plasma factor activity must be <30% for prolongation of aPTT test



Patient Plasma	**Normal Pooled Plasma**	**1:1 mixed plasma**
Factor activity 0-10%	Factor activity 80-100%	Factor activity 40-50 %
PTT: 72 sec	PTT: 32 sec.	PTT: 32 sec.

Mixing Test

Pp PTT
72 sec

+

Np PTT
32 sec

Factor deficiency

→ Mixing: PTT
Time 0: 33 sec

→ 30 min: 33 sec

→ 60 min: 33 sec

→ 120 min: 35 sec

Pp: Patient's plasma, Np: Normal pooled plasma

Mixing Test

Pp PTT
72 sec

+

Np PTT
32 sec

Factor inhibitor

→ Mixing: PTT
Time 0: 33 sec

→ 30 min: 40 sec

→ 60 min: 51 sec

→ 120 min: 72 sec

Pp: Patient's plasma, Np: Normal pooled plasma

Mixing Test

Pp PTT
72 sec

+

Np PTT
32 sec

→ Mixing :PTT
Time 0: 70 sec

→ 30 min: 70 sec

Lupus Anticoagulant → 60 min: 71 sec

→ 120 min: 73 sec

Pp: Patient's plasma, Np: Normal pooled plasma

Lupus anticoagulant: Phospholipid dependency

Pp PTT

72 sec

+

Phospholipids

(hexagonal or platelet derived)

→

PTT: 32 sec

-It is necessary to demonstrate that there is no specific factor deficiency

A 24-year-old female patient with prolonged PTT

- **Lupus anticoagulant test was positive with both PTT and diluted Russell Viper Venom time (dRVVT)**
- **Anti-cardiolipin IgG: 120 GPL, IgM: 6.4 MPL**
- **Anti-Beta2 GPI IgG: 116 IU/l, IgM: 5.6 IU/l**
- Anti-nuclear antibody (ANA) and anti-dsDNA were negative

Triple positive aPL profile

A 24-year-old female patient with prolonged PTT

- She had no history of thrombosis or fetal loss
- No history of arthritis, lupoid rash, oral ulcers
- Lymphocyte count, complement levels, creatinine, urine analysis were normal
- No **definite** 'Antiphospholipid Syndrome (APS)' or 'Systemic Lupus Erythematosus (SLE)' diagnosis

A 24-year-old female patient with *triple aPLA*

Recommendations:

- Repeat the antiphospholipid antibody tests after 12 weeks
- Stop smoking
- Be aware of clotting symptoms
- Informed about situations that may increase the risk of thrombosis (eg hormone use, long journeys, high-risk surgical operations)

Should she receive primary prophylaxis for thrombosis?

EULAR recommendations for the management of antiphospholipid syndrome in adults

Low-risk aPL profile:

- Isolated aCLA or antibeta2 GPI antibodies at low –medium titres

High-risk aPL profile:

- The presence of LA, or of double (any combination of LA, aCLA or antibeta2 GPI antibodies or **triple (all three subtypes) aPL positivity**, or the presence of persistently high aPL titres.

Medium-high aPL titres:

- aCLA of IgG and/or IgM titres >40 GPL/MPL units, or >the 99th percentile
- Antibeta2-GPI IgG and/or IgM titres >the 99th percentile.

Tektonidou MG, et al. Ann Rheum Dis 2019;78:1296–1304

EULAR recommendations for the management of antiphospholipid syndrome in adults

In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with low-dose aspirin (LDA) (75–100 mg daily) is recommended

Tektonidou MG, et al. Ann Rheum Dis 2019;78:1296–1304

A 24-year-old female patient with high risk aPL profile: Surgical operation

Recommendations:

- Repeat the antiphospholipid antibody tests after 12 weeks
- Stop smoking
- Be aware of clotting symptoms
- Informed about situations that may increase the risk of thrombosis (eg hormone use, long journeys, high-risk surgical operations)
- **Primary thrombosis prophylaxis with aspirin 81 mg/day**

Is septum deviation surgery safe for her?

EULAR recommendations for the management of antiphospholipid syndrome in adults

aPL-positive individuals should use LMWH in high-risk situations such as surgery, hospitalisation, prolonged immobilisation and the puerperium.

Tektonidou MG, et al. Ann Rheum Dis 2019;78:1296–1304

A 24-year-old female patient with high risk aPL profile: Surgical operation

- Surgical operation for nasal septum deviation does not require hospitalisation, has no increased risk for thrombosis: the patient did not receive LMWH prophylaxis

Does prolonged PTT increase the risk of bleeding during surgery?

A 24-year-old female patient with high risk aPL profile: Surgical operation

- In patients with LA, prolonged PTT does not cause abnormal bleeding unless severe thrombocytopenia, coexistence of other coagulation abnormalities, or the presence of anti-prothrombin antibodies

Anti-prothrombin antibodies

- Anti-prothrombin antibodies are commonly found in patients with APS
- Mostly, these antibodies do not correlate with thrombosis
- In rare cases, anti-prothrombin antibodies may decrease prothrombin activity or enhance prothrombin clearence, and cause bleeding
- If an APS patient has unexplained prolonged prothrombin time (PT) test, anti-prothrombin antibodies should be considered

Sciasci S, et al, Thromb Haemost 2014: 111:354-64
Bajaj SP et al, Blood 1983; 61:684-92

References:

- Tektonidou MG, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 2019;78:1296–1304.
- Devreese KMJ et al. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost.* 2020;18:2828–2839.
- Erkan D, Lockshin MD (editors): Antiphospholipid Syndrome. Current Research Highlights and Clinical Insights. *Springer Publishing,* 2017