Lupus anticoagulant in an elderly woman with dementia: a clinical case report with many questions and few answers

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Abstract

We describe the clinical case of an elderly woman with dementia, suffering from bilateral soleal venous thrombosis, despite antithrombotic prophylaxis, after orthopedic surgery. An isolated anti-cardiolipin antibodies positivity, however pre-existing for at least seven years, was found in a patient with previous cerebral ischemia and treated intermittently with aspirin. During the coronavirus disease 2019 (COVID-19) pandemic lockdown, to promote patient compliance, we practiced anticoagulant therapy with edoxaban: resolution of venous thrombosis was achieved. Long-lasting medical treatment is discussed.

Introduction

Why do we describe this case?

Even a modest alteration in laboratory tests can conceal a serious illness. This is the case of the elongated activated partial thromboplastin time (aPTT) which is compatible with the antiphospholipid antibody syndrome (APS). This syndrome, associated with a thrombotic pathology, more frequent at a young age, presents itself with multiple aspects, and must be confirmed with more in-depth and repeated laboratory tests in the context of autoimmunity. It should also be taken into consideration in the geriatric age.

An elongated aPTT is compatible with the presence of lupus anticoagulant (LAC), the positivity of which represents one of the criteria for defining the APS. This syndrome is the most common acquired thrombophilia, a systemic autoimmune disease characterized by vascular thrombosis and obstetric morbidity mediated by antiphospholipid antibodies (aPL), including LAC, anti-cardiolipin antibodies (aCL) and anti-b2-glicoprotein I antibodies (antiβ2GPI). Most patients with APS are diagnosed between the ages of 15 and 50.[1] APS can manifest as an isolated disease (primary APS) or associated with other systemic autoimmune diseases (secondary APS), such as systemic lupus erythematosus (SLE). Patients with onset of APS in the geriatric age are more frequently male, carriers with a higher frequency of stroke, angina pectoris[1] and LAC.[2-6]

Case Report

In the acute period of the coronavirus disease 2019 (COVID-19) pandemic, a 75-year-old woman is transferred from the Orthopedics Department to the Rehabilitation unit after hip endoprosthesis following a post-traumatic fracture of the right femoral neck. The postoperative course was complicated by the onset of agitation, disorientation, hallucinations and confabulations, symptoms which required antipsychotic treatment with promazine, haloperidol, risperidone and quetiapine.

The anamnesis showed: no smoking or alcohol, appendectomy, juvenile migraine, carpal tunnel surgery, contact dermatitis, microscopic lymphocytic colitis, hypercholesterolemia (total cholesterol with maximum value 267 mg/dL, low-density lipoprotein 197 mg/dL), small euthyroid goiter, osteoporosis, hepatic steatosis, biliary cysts, multiple microcholelithiasis. Five years earlier she underwent left hip endoprosthesis for femoral neck fracture: she was treated with antithrombotic prophylaxis by enoxaparin 4000 UI/day.

At the age of fifty, an anxious-depressive syndrome developed then evolved into fronto-temporal dementia (FTD) associated with behavioral disturbances. Ten years earlier he had presented a transient hemiparesis: the cerebral computed tomography (CT) showed hypodense lacunae in the left parietal and right frontal area. Carotid ultrasound: eccentric hyperechoic plaque, with regular surface, in the right internal carotid artery without significant stenosis. Since then, she has taken oral aspirin 100 mg/day. A CT scan performed two years later showed an additional hypodense area in the left frontal area (Figure 1).

The patient was receiving therapy with oral duloxetine 60 mg/day only (not aspirin), but irregularly. On physical examination, metal sutures were present on the right hip in the site of subfascial hematoma, remaining normal objectivity, blood pressure 120/70 mmHg. Chest X-ray: aortosclerosis only. Electrocardiogram: sinus rhythm 66/min, QTc 424 sec.

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Key words: Antiphospholipid syndrome; lupus anticoagulant; venous thrombosis; frail elderly; direct oral anticoagulants; edoxaban.

Contributions: MT provided the clinical data and has written the text; AA and IC provided clinical data.

Funding: this article has been published without the support of sponsors.

Conflict of interest: the authors declare no potential conflict of interest.

Consent to publication: consent was obtained for the publication of this clinical case.

Received for publication: 22 April 2022.
Revision received: 14 July 2022.
Accepted for publication: 6 September 2022.

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Geriatric Care 2022; 8:10571
doi:10.4081/gc.2022.10571

Laboratory tests showed (Table 1): platelets 505-318×10.9/L, aPTT: 54-52.2 sec (nv: 26-36), ratio 1.69-1.63 (nv: 0.82-1.19), international normalized ratio (INR) and fibrinogen normal; folate: 2.4 ng/mL (nv: 3.0-17), vitamin B12: 143 pg/mL (nv: 193-982), 25-OH Vitamin D: 17 nmol/L (deficiency: <50), total cholesterol: 206 mg/dL, TSH: 8.39 mUI/L (nv: 0.34-4.20), fT4 normal, Ab anti-TGB: 6 IU/mL (nv: 0-4), Ab-anti TPO: 110 IU/mL (nv: 0-9); CA-125 and CEA normal. All other routine blood chemistry were within normal limits. COVID-19 rhino-pharyngeal swab negative.

Thyroid ultrasound (US) showed a slightly reduced gland, with an inflammation-worm-like echostructure, a 4 mm nodule in the lower right pole, and colloid-cystic features in the left lobe.

After temporarily stopping antithrombotic prophylactic therapy (subcutaneous

enoxaparin 4000 UI/day), and with heparinemia absent, the presence of Lupus Anticoagulant was sought with a positive result (Table 2).

We found a marked increase in D-dimer (Table 2) not associated with objective alterations of the lower limbs in the presence of gradually compressive elastic stockings. A venous Doppler US was required with the following result: bilateral isolated distal deep vein thrombosis (IDDVT) involving 4 soleal veins (SV) with diameter thickness 4 mm. Therapy with subcutaneous enoxaparin was increased to 8000 UI/bid, then replaced by oral edoxaban 60 mg/day. A D-dimer check after 5 days of anticoagulant therapy showed a marked decrease to 1205 µg/L.

Additional therapy at home: levothyroxine 25 µg/day, cholecalciferol 50.000 IU/week, intramuscular cyanocobalamin 1000 µg/week, folate 5 mg/day, quetiapine 25 mg/bid, perphenazine 4 mg/day, alendronic acid 70 mg/week.

After three months the venous Doppler US check showed a good recanalization of the soleal veins and a residual thickness of the coagulum of 2 mm. Therefore, edoxaban therapy was suspended. aPTT control after one year was 51.4 sec (ratio 1.51).

Table 1. Summary table of the first level laboratory tests performed.

Parameters	Detected levels	Normal range
Aspartate amino transferase (U/L)	16	<35
Alanine amino transferase (U/L)	10	<45
γGT (U/L)	19	3-55
Alkaline phosphatase (U/L)	77	33-98
Sodium (mEq/L)	137	136-145
Potassium (mEq/L)	3.6	3.5-5.0
LDH (U/L)	148	0-250
C-reactive protein (mg/L)	0.28	<5
ESR (mm/h)	33	<30
Creatinine (mg/dL)	0.6	0.5-1.0
Total cholesterol (mg/dL)	206	<220
Triglycerides (mg/dL)	98	<180
Calcemia (mg/dL)	9.2	8.5-10.5
Phosphorus (mg/dL)	4.0	3.0-5.0
Uricemia (mg/dL)	3.9	2.0-5.0
Red blood cells ($\times 10^{12}$/L)	4.34	3.85-5.20
Hemoglobin (g/L)	135	135-160
MCV (fL)	88.1	80-100
PLTs ($\times 10^{9}$/L)	505-318	160-370
White blood cells ($\times 10^{9}$/L)	4.63	3.60-10.50
Neutrophils ($\times 10^{9}$/L)	2.12	1.50-7.70
Total protein (g/dL)	6.9	6.0-8.4
Albumin (%) (g/dL)	 54.1 3.6	 55.0-67 3.5-5.2
Alpha-1-globulins (%)	5.4	2.5-5.0
Alpha-2-globulins (%)	12.6	6.0-12
Beta-1-globulins (%)	6.3	5-7.5
Beta-2-globulins (%)	5.4	3.5-7.0
Gamma-globulins (%)	16.2	11-20
aPTT (sec) ratio	 54-52.2 1.69-1.63	 26-36 0.82-1.19
Prothrombin time-INR ratio	1.14	0.90-1.20
Fibrinogen (mg/dL)	368	200-400
TSH (mUI/L)	8.39	0.34-4.20
Free-T4 (ng/dL)	0.75	0.54-1.20
Anti-TGB-Ab (IU/mL)	6	0-4
Anti-TPO-Ab (IU/mL)	110	0-9
TSHR-Ab (U/L)	<0.27	<0.80
Folate (ng/mL)	2.4	3.0-17
Vitamin B12 (pg/mL)	100.7	193-982
CEA (ng/mL)	0.6	0-30
CA-125 (U/mL)	8	0-35
25-OH Vitamin D (nmol/L)	17	Deficiency: <50
COVID-19 rhino-pharyngeal swab	Negative	-

aPTT, activated partial thromboplastin time; TSHR-Ab, anti-TSH-receptor antibodies; Anti-TPO Ab, anti-thyroperoxidase antibody; Anti-TG Ab, anti-thyroglobulin antibody.

Discussion

We described the postoperative course for femur fracture of an elderly woman with cognitive impairment and behavioral disturbances, carrier of multivitamin deficiency and autoimmune subclinical hypothyroidism, in which isolated aCL was found. The bilateral IDDVT finding was completely 'occasional' because it was suggested only by an elevated D-dimer despite antithrombotic prophylaxis. This prophylaxis with LMVH (enoxaparin 4000 IU/day) was not sufficient to prevent the onset of IDDVT in a subject with isolated LAC (aCL-, aβ2GPI-), immobilized after

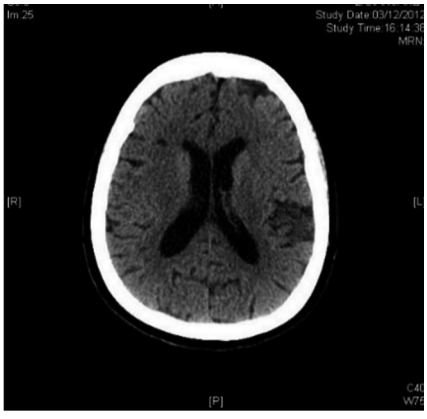

Figure 1. Brain computed tomography (2012). In the left frontal area, hypodense areola of about 6 mm; mild hypodensity, from previous ischemic outcomes, in the left parietal area.

orthopedic surgery. A retrospective investigation of past laboratory tests in 2009 revealed normal aPTT (33.5 sec, ratio 1.06), LAC positivity (aPTT: 41.1 sec, ratio 1.38) already seven years earlier. The patient was treated with ASA 100 mg/day for at least four years, but the intake was completely irregular. During this long period, no signs of autoimmune disease appeared.

Lupus anticoagulant as the most valuable biological marker of antiphospholipid syndrome in the elderly[2] and its isolated positivity is associated with a high risk of thrombosis, both arterial and venous,[3] although the data of the literature are contradictory regarding the single positivity.[4-7] Based on the 2019 EULAR recommendations, vitamin K antagonists (VKAs) still remain the primary treatment for preventing recurrent events in individuals with APS.[8] The use of direct acting oral anticoagulants (DOACs) in patients with APS is still controversial, and the identification of specific APS patients who might benefit from this therapy is still an open question,[9] although efficacy has been demonstrated in the low-risk subgroup,[10] unlike triple positivity aPL (LAC, aCL, aβ2GPI) and/or arterial thrombi.[11-13] Triple positive patients are in fact patients at much higher risk than those with double or single positivity.[14]

An increased risk of recurrent thromboembolism has also been recently described in a small group of patients with low-risk APS, positive for single or double antibody, treated with rivaroxaban compared to conventional therapy with warfarin.[15]

In our case, the antiphosphatidylserine/prothrombin antibody assay, which cannot be performed in our laboratory, could better define the thrombotic risk and the prolongation of anticoagulant therapy, since isolated aCL is invariably associated with positive aPS/PT.[7,16-18] The positive antinuclear antibody (ANA) finding, given the increased frequency in the elderly population, could characterize our patient in a subgroup of subjects at higher thrombotic risk, but without being associated with lupus evolution.[19]

According to the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) informative note of 20 May 2019 DOACs are not recommended in patients with APS.[20] A practical guide for healthcare professionals related to the management of patients with APS has recently (2020) been published from the International Society on Thrombosis and Haemostasis (ISTH).[21] In Italy in October 2021 the guidelines of the Lombardy Region were drawn up.[22] The use of DOACs in APS should be limited to special cases of patients with venous thromboembolism and contraindication to VKA (intolerance or allergy), difficulty in maintaining the INR in the therapeutic range despite good adherence to the VKA treatment, low risk antibody profile.

In our frail elderly patient with objective difficulties to access regular monitoring of INR during the COVID-19 pandemic lockdown, as an alternative to the indefinite duration of VKA therapy, anticoagulant treatment with full dose edoxaban was practiced promoting compliance with a single administration independent of food intake.

It should be noted that a recent Italian study on real-life experience during that viral pandemic[23] demonstrated the efficacy and safety of edoxaban in preventing recurrence of unprovoked VTE/PE in patients with isolated aCL positivity. This series, however small (30 patients) and limited in the follow-up to 8-9 months, refers to warfarin-shifted subjects, not elderly (mean age: 53.3 years), in which antinuclear antibodies have not been defined.

Table 2. Coagulation, immunological and autoimmunity studies.

Coagulation studies test	Detected level	Measure units	Normal range
D-dimer	2247	g/L (FEU)	0-500
Antithrombin	104	%	75-125
Heparinemia in plasma	0.00	UI/mL	Absent
LAC DRVVT test			
DRVVT screen test	2.20	Ratio	<1.20
DRVVT correction test	1.64	Ratio	<1.20
DVRRT confirm test	1.84	Ratio norm	<1.20
LAC PTT LIKE test	SCT		
SCT screen test	3.56	Ratio	<1.20
SCT correction test	2.00	Ratio	<1.20
SCT confirm test	3.41	Ratio	<1.20
Immunological studies test	**Detected level**	**Measure units**	**Normal range**
IgG aCL	0.8	GPL-U/mL	Negative <10
IgM aCL	5.5	MPL-U/mL	Negative <10
IgG a 2-GPI	1.2	U/mL	Negative <7
IgM a 2-GPI	1.9	U/mL	Negative <7
Autoimmunity studies test	**Detected level**	**Measure units**	**Normal range**
Rheumatoid factor	<10	UI/mL	<14
ANA, granular pattern	Positive 1:160	IFI	<1:80
Anti-ENA screening	0.3	Ratio	Negative <0.7
c-ANCA	anti-PR3: <0.1	UI/mL	Negative <2
p-ANCA	Anti-MPO: 0.3	UI/mL	Negative <3.5

LAC, lupus anticoagulant; SCT, silica clotting time; dRVVT, diluted Russell viper venom time; IgG aCL, anti-cardiolipin IgG antibody; IgM aCL, anti-cardiolipin IgM antibody; GPL, IgG antiphospholipid units, refers to IgG phospholipid units; MPL, IgM antiphospholipid units, refers to IgM phospholipid; IgG a 2-GPI, anti-b2-glicoprotein I-IgG antibody; IgM a 2-GPI, anti-b2-glicoprotein I-IgM antibody; FEU, fibrinogen equivalent units; ANA, anti-nuclear antibody; IFI, indirect immunofluorescence; ENA, extractable nuclear antigen; c-ANCA, anti-neutrophil cytoplasmic autoantibodies; p-ANCA, perinuclear anti-neutrophil cytoplasmic autoantibodies; anti-MPO, anti mieloperossidase antibodies; anti-PR3, anti proteinase 3 antibodies.

Conclusions

At the present time there are no clinical cases similar to ours treated with edoxaban indefinitely in the literature. Our case report leaves some issues unresolved: i) the possible use of hydroxychloroquine therapy in an elderly with isolated LAC and positive ANA; ii) the possible use of low-dose aspirin with or without anticoagulant therapy with edoxaban; iii) the anticoagulant therapy duration: long life?

Key points

- The positivity of LAC can be isolated or associated with the positivity of other antibodies (aCL, aβ2-GPI).
- An isolated LAC can be associated with thrombotic phenomena, but it may not be associated with overt autoimmune diseases.
- In the presence of thrombotic, arterial and/or venous, complications, anticoagulant treatment with VKAs is indicated. DOACs is currently unauthorized but can only be considered for exceptional cases.

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