OPIS PRZYPADKU

# Primary antiphospholipid syndrome – – case report

## Pierwotny zespół antyfosfolipidowy – opis przypadku

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ABSTRACT

INTRODUCTION

Antiphospholipid syndrome (APS) is one of the most common thrombocytophilias; unfortunately, it is not recognized often enough. 2–5% of the population suffering from APS syndrome has an increased level of antiphospholipid antibodies and in 30–50% of those persons, the symptoms of APS may occur. The lack of proper prevention in undiagnosed patients causes severe complications and the most frequent reasons for mortality in those patients include cerebral stroke, intracerebral haemorrhage, encephalopathies, acute coronary syndromes and infections.

CASE HISTORY

A 27 year-old woman with hypercoagulability of the blood, who presented recurrent incidents of venous-arterial thrombosis including a left-side pulmonary embolism is described. One year before an actual hospitalization, the patient suffered from venous thrombosis of the left lower limb, complicated by left-sided pneumonia with accompanying exudative pleurisy and subsequent constant dyspnea. Based on an updated diagnostic algorithm she was diagnosed as having primary APS and was successfully treated.

CONCLUSIONS

The present case suggests that APS should be considered in every case of hypercoagulability of the blood with recurrent thrombosis at an atypical localization or of an atypical etiology. The initial diagnosis could be confirmed by determination of anticardiolipin antibodies classes IgM and IgG, with verification after 3 months. Constant anticoagulant treatment maintaining the International Normalized Ratio (INR) in the range of 2.0–3.0 not only enables the subsidence of symptoms without any time-limit, but also in the case of serious complications such as a pulmonary embolism, but also prevents recurrent incidents of venous-arterial thrombosis in the future.

KEY WORDS

antiphospholipid syndrome, recurrent thrombosis, anticardiolipin antibodies, anticoagulant therapy

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## STRESZCZENIE

### WSTĘP

Zespół antyfosfolipidowy (APS) będący jedną z najczęstszych trombocytofilii, nie jest, niestety, rozpoznawany dostatecznie często. Podwyższony poziom przeciwciał antyfosfolipidowych w surowicy ma 2–5% populacji pacjentów z zespołem APS, a u 30–50% z nich mogą wystąpić objawy tego zespołu. Brak właściwej prewencji u pacjentów niezdiagnozowanych może prowadzić do poważnych powikłań. Najczęstszymi przyczynami śmiertelności u tych chorych są: udar mózgowy, krwotok śródczaszkowy, encefalopatie, ostre zespoły wieńcowe oraz infekcje.

### OPIS PRZYPADKU

W pracy opisano 27-letnią pacjentkę z nadkrzepliwością krwi i nawracającymi epizodami zakrzepicy żylno-tętniczej, w tym zatorowością lewego płuca. Rok przed obecną hospitalizacją u pacjentki wystąpiła zakrzepica żylna lewej kończyny dolnej, powikłana przez lewostronne zapalenie płuca z towarzyszącym odczynem opłucnowym i następczą trwałą dusznością. Opierając się na aktualnym algorytmie diagnostycznym, rozpoznano u pacjentki pierwotny zespół antyfosfolipidowy, który poddano skutecznemu leczeniu.

### WNIOSKI

Przedstawiony przypadek sugeruje, że pierwotny zespół antyfosfolipidowy powinien być rozważany w każdym przypadku nadkrzepliwości krwi z nawracającymi epizodami zakrzepicy o nietypowej lokalizacji i etiologii. Wstępne rozpoznanie może być potwierdzone poprzez oznaczenie stężenia przeciwciał antykardiolipinowych klas IgM i IgG, z weryfikacją po 3 miesiącach. Przewlekłe leczenie przeciwkrzepliwe utrzymujące wartość wskaźnika INR w zakresie 2,0–3,0 zapewnia nie tylko nieograniczone czasowo ustąpienie objawów klinicznych, również w przypadku poważnych powikłań jak zatorowość płucna, ale także zapobiega występowaniu nawracających epizodów zakrzepicy żylno-tętniczej w przyszłości.



### SŁOWA KLUCZOWE

zespół antyfosfolipidowy, nawracająca zakrzepica, przeciwciała antykardiolipinowe, leczenie przeciwkrzepliwe


## INTRODUCTION

Antiphospholipid syndrome (Hughes's syndrome, APS) is a non-inflammatory autoimmunological disease. It is one of the most common acquired thrombocytophilias.

This syndrome was described in 1983 by Graham RV Hughes as a complex clinical syndrome, characterized by thrombosis, recurrent spontaneous abortion, neurological disease and so-called lupus anticoagulant, which was identified as circulating anticardiolipin antibodies [1]. As the antibodies determined in those patients reacted also with other phospholipids, the name of the syndrome was changed to the primary antiphospholipid syndrome. The first patient with a full primary antiphospholipid syndrome was presented in 1982 [2].

APS syndrome is caused by antiphospholipid antibodies (aPL) class IgM, IgG or IgA against proteins connected with negatively charged phospholipids (for example prothrombin, protein C, protein S, factor X and XI, annexin V), macromolecular kininogen, beta 2-glycoprotein and platelet receptors [3,4,5].

The etiopathogenesis of APS is still not well known. It is supposed that antiphospholipid antibodies modify or activate the coagulation process and cause thrombotic-embolic incidents in various organs (if they occur in more than three organs the disease is classified as severe – so called catastrophic antiphospholipid syndrome). Moreover, antiphospholipid antibodies bind endothelium beta 2-glycoprotein causing an augmented production of inflammatory cytokines and adhesive molecules [3,4,5].

It seems that the possible mechanisms of thrombosis are numerous and they include the binding of aPL to platelets and endothelial cells resulting in the induction of procoagulant proteins or adhesion molecules by these cells. In consequence, anionic phospholipids are exposed on cell surfaces, which are covered by phospholipids-binding proteins, such as beta 2-glycoprotein or prothrombin (so called "co-factor"). When antibodies bind these proteins or protein-phospholipid complexes, the induction of the production of procoagulant substances such as the tissue factor, plasminogen acti-

vator inhibitor or adhesion molecules occurs, resulting in activation of the thrombosis process [6].
The actual frequency of incidence of APS in the general population is unknown. APS is more common in young to middle-aged adults (especially in 50–60 year-old age group) and a female predominance has been documented, particularly for secondary APS. Women suffer from APS twice as frequently as men [3,4,5].
The typical symptoms of APS include recurring incidents of peripheral venous-arterial thrombosis, often accompanied by multiple leg and arm vein thrombosis and coronary infarction or rethrombosis after bypass surgery (more than 40% of patients with acute coronary syndrome have anticardiolipin antibodies), transient cerebral ischaemic incidents and progressive cerebral ischaemia (up to 60% of patients with thrombosis of the central nervous system suffer from APS), thrombocytopenia (usually above 50 G/l), obstetric adversities (multiple spontaneous abortions), and also cutaneous lesions such as livedo reticularis most often located on the knees [7,8,9,10]. In some patients, other features occur such as fluctuating blood pressure, headaches (often migrainous and intractable), epilepsy or abnormal EEGs (often going back to early teen years) [11], visual field defects, dementia, pulmonary hypertension, Budd-Chiari syndrome and renal vein thrombosis [2,6].
Definite diagnosis of antiphospholipid syndrome requires fulfilling at least one clinical criterion and one laboratory criterion [Sapporo (1999); modified at Sydney (2006)] [12].
The clinical criteria are as follows:

– Vessel thrombosis – one or more episodes of thrombosis of an artery, vein (besides superficial venous thrombosis) or capillary vessels in a tissue or an organ, confirmed by ultrasonographic and color Doppler imaging or histological examination (in histopathological slide, inflammatory vessels should not be seen) [13].
– Obstetric adversities:
  a) 1 necrobiosis of a morphologically normal fetus after $10^{th}$ week of pregnancy (normal morphology of fetus documented by ultrasonographic or direct sectional examination), or
  b) 1 premature delivery of a morphologically normal newborn before $34^{th}$ week of pregnancy in connection with preeclampsia or eclampsia or a severe failure of the placenta, or
  c) 3 idiopathic, unexplained miscarriages before $10^{th}$ week of pregnancy, excluding cases connected with mother's anatomic or hormonal disorders or both parents' chromosome disorders.

Laboratory criteria – a positive result detected ≥ 2 times in a 12 week interval for:

– lupus anticoagulant present in the plasma (prolonged phospholipids-dependent coagulation times, e.g. Activated Partial Thromboplastin Time (APTT), are typical for lupus anticoagulant, though in vivo they cause thromboses). When the lupus anticoagulant is present, APS is qualified as a secondary syndrome [14].
– anticardiolipin antibodies class IgG or IgM present in the serum or plasma, in medium or high concentration (antibodies class IgM in a low concentration may be positive in patients with neoplasm, some infection or those treated with hemodialysis or with some specific drugs, but in those cases they do not cause thrombosis) [5,8,10].
– antibodies against beta 2-glycoprotein present in serum or plasma (titer > 99 percentile) [5].

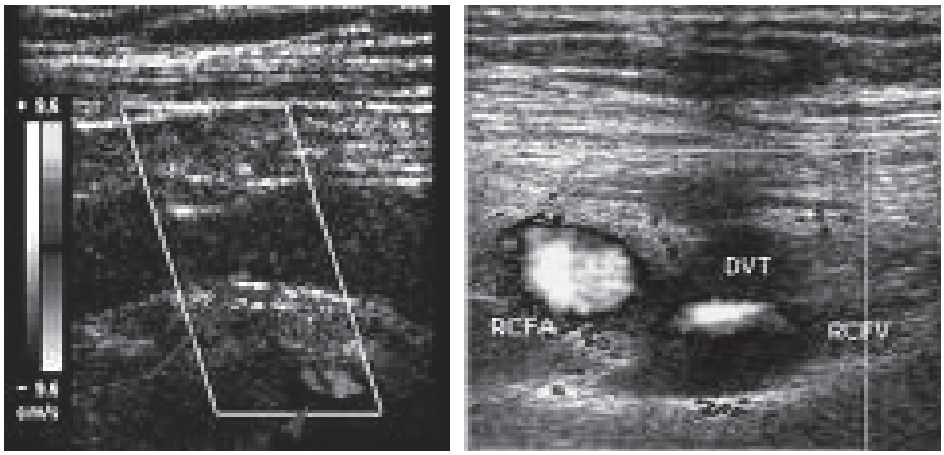
These criteria do not concern clinical situations when the symptoms appear in a term shorter than 12 weeks or longer than 5 years from the moment the diagnosis of APS is established.

## CASE REPORT

A 27-year-old woman was admitted to the Department and Clinic of Internal Diseases, Angiology and Physical Medicine of the Medical University of Silesia in Bytom in order to diagnose the specific causes of blood hypercoagulability.
She was a smoker (8 cigarettes per day for the last 4 years), physically active, after 2 pregnancies ended by a cesarean section, without any medical history of injuries requiring immobilization of the lower extremities. So far, she had not take any hormonal contraception.
In anamnesis: 1 year ago the patient suffered from venous thrombosis of the left lower limb treated with *enoxaparine* in a dose of 0,4 ml/day. 1 month before the hospitalization she was an ambulant patient with a suspicion of left-sided pneumonia with accompanying exudative pleurisy treated with *doxycyclinum* in a typical curative dose. Since then she has been complaining of constant dyspnea and low effort tolerance.
In the course of the hospitalization, the patient was in a good general condition without any ailments. In the physical examination no pathological symptoms were found, except for single crepitation at the base of both lungs disappearing after deep respiration.

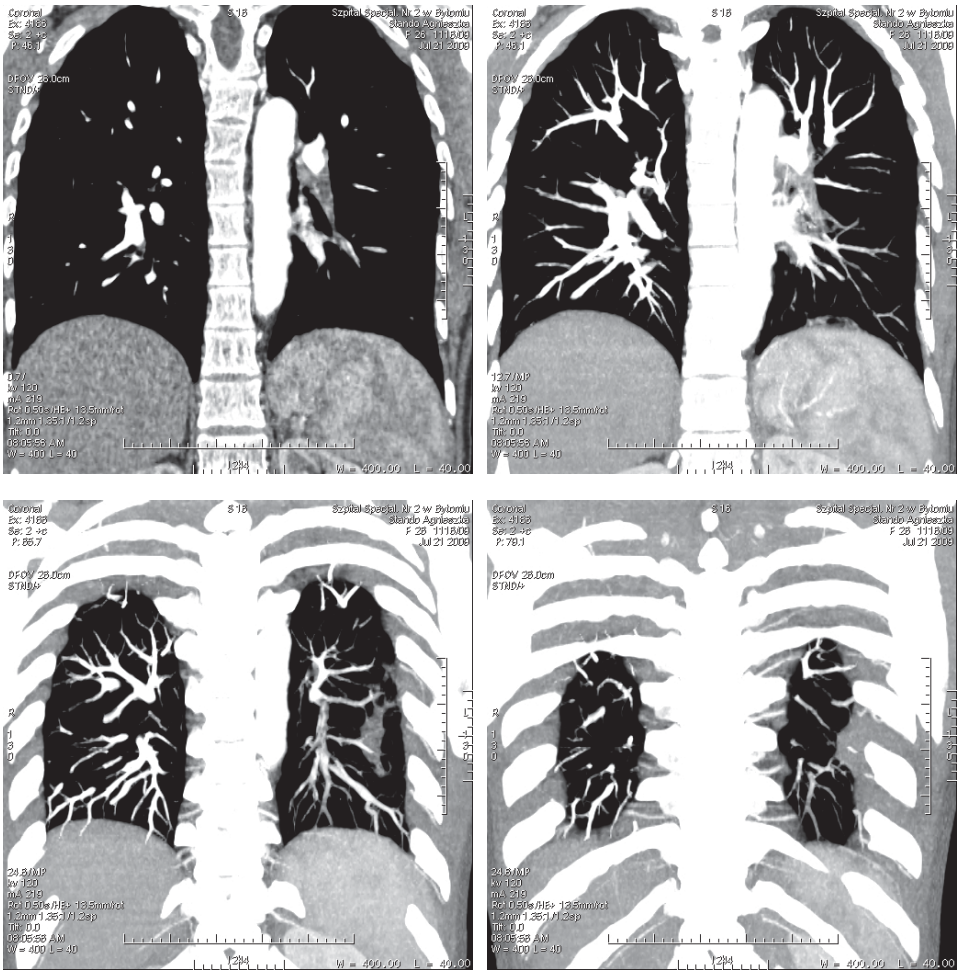
**Laboratory analysis:**

– blood erythrocyte sedimentation rate after 1 hour: 29 mm,
– APTT 25.2 s (reference range: 26–36 s), prothrombin index 69.0% (reference range: 70–120%), prothrombin time 14,6 s (reference range: 10.4––14.4 s),
– anticardiolipin antibodies IgG 102.4 U/ml (N < 12 negative result),




A B

Fig. 1A-B. UDP of lower limbs: visible left femoral vein in phase of recanalization, with mural thrombus narrowing lumen of vessel up to 50% (RCFA – – right commune femoral artery, DVT – deep vein thrombus, RCFV – right commune femoral vein).
Ryc. 1A-B. UDP kończyn dolnych: widoczna lewa żyła udowa w trakcie rekanalizacji ze skrzepliną przyścienną zwężającą światło naczynia do 50% (RCFA – prawa tętnica udowa wspólna, DVT – skrzeplina żyły głębokiej, RCFV – prawa żyła udowa wspólna).



A B C D

Fig. 2A-D. Angio-CT of pulmonary arteries: visible normal pulmonary trunk and right pulmonary artery with branching – on left side mural thrombus in branching of left pulmonary artery and 6th segmental artery, parenchymal mural condensation in lung and post-inflammatory lesion in costophrenic angle.
Ryc. 2A-D. Angio-TK tętnic płucnych: widoczny prawidłowy pień płucny oraz prawa tętnica płucna z rozgałęzieniami – po stronie lewej skrzeplina przyścienna w miejscu rozgałęzienia lewej tętnicy płucnej oraz w tętnicy segmentowej 6, przyścienne zagęszczenie w miąższu płucnym i zmiany pozapalne w kącie przeponowo-żebrowym.

– anticardiolipin antibodies IgM > 120 U/ml (N < 12 negative result),

Syphilis reagin causing a false positive result of the Veneral Disease Research Laboratory (VDRL) test and antinuclear antibodies (ANA) were absent. Blood cell count, serum concentrations of D-dimer, fibrinogen, AT III antithrombin, C Reactive Protein, glucose, creatinine, urea, uric acid, protein, bilirubin, thyroid-stimulating hormone, natrium and kalium, as well as serum activity of glutamic oxoloacetic transaminase (GOT) and glutamic pyruvic transferase (GPT) were within the reference range. The International Normalized Ratio (INR) value and urine analysis were within the reference range, as well. Electrocardiography and ultrasonographic examination of abdominal cavity were normal.

**Instrumental examination**

– Chest radiogram: left sided diaphragm-pleural adhesions, band-shaped shadow on the left lung, which seemed to be pleural thickening. Profile of the heart – normal.
– Doppler ultrasound imaging (UDP) of the lower limbs (Fig. 1A-B): Left femoral vein and left popliteal vein in the phase of recanalization, with a mural thrombi narrowing lumen of the vessel up to 50%, VSM, VSP unobstructed, without thrombus. The venous system of the right lower limb normal.
– Computed tomographic angiography (Angio-CT) of the pulmonary arteries (Fig. 2A-D): Pulmonary trunk, right pulmonary artery with normal branching. On the left side a mural thrombus in the branching of the left pulmonary artery and 6 segmental artery. Parenchymal mural condensation in the left lung and a post-inflammatory lesion in the left costophrenic angle.

On the basis of the clinical examination as well as the results of laboratory analyses and instrumental examinations, according to the afore-mentioned criteria the initial diagnosis in the case study was thromboembolic disease with a left-side pulmonary embolism in the course of primary antiphospholipid syndrome.

The treatment included *Enoxaparin sodium*, *Acenocoumarol*, *Diosmin*, *Hesperidine*, anti-nicotine therapy and varicose stockings resulting in subsidence of the symptoms of respiratory insufficiency and crepitation at the base of both lungs in a physical examination as well as improvement in effort tolerance.

The patient was discharged from hospital with recommendation of treatment with *acenocumarol* in a dose of 2 mg per day – to keep INR in the range of 2.0–3.0, without a time-limit.

The patient was informed that antiphosholipid syndrome is a risk factor of thrombosis recurrence, especially if she stops the anticoagulant therapy or takes hormonal contraception. After 3 months the IgG anticardiolipin antibodies level was verified and the initial diagnosis was confirmed.

## DISCUSSION

Though APS is one of the most common thrombocytophilias, unfortunately, it is not recognized often enough [15]. The lack of proper prevention in undiagnosed patients causes severe complications and the most frequent reasons for mortality in those patients include a cerebral stroke, intracerebral haemorrhage, encephalopathies (27%), acute coronary syndromes (19,8%) and severe infections (19,8%) [16].

It should be remembered that 2–5% of the population has detectable anticardiolipin antibodies. In 30–50% of those persons the symptoms of APS may occur. That is why in every case of recurring thrombosis, especially in an atypical localization or an atypical etiology, APS should be considered [17].

Contemporary optimal treatment of APS, especially in the case of the catastrophic form, has three main aims: to treat any precipitating factors (prompt use of antibiotics if infection is suspected, amputation of any necrotic digits, high awareness in patients with APS who undergo an operation or an invasive procedure), to prevent and treat ongoing thrombotic events as well as to suppress excessive cytokine action. The most commonly applied therapy includes anticoagulation (usually intravenous heparin followed by oral anticoagulants), corticosteroids, plasma exchange, intravenous gammaglobulins and, if associated with lupus flare, cyclophosphamide [18].

Anticoagulant therapy of anunlimited duration should be recommended in patients with a diagnosed APS. According to actual consent in prevention of therecurrence of thrombotic-embolic disease maintaining INR in the range of 2.0–3.0 gives equal results as in the range of 3.1–4.0 [19]. Not smoking and avoiding the hormonal contraception in those patients is also of a great importance.

So far, the management of patients with APS has been mainly supportive, generally aimed at avoiding recurrent thrombotic events. It seems that therapy targeted at the triggering factor (antiphospholipid antibodies) including a combination of plasmapheresis, which reduces the serum antibodies level, and anti-CD20 antibody (*rituximab*), which inhibits their production, could offer a promising perspective [20].

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