

ANTIPHOSPHOLIPID SYNDROME IN A YOUNG PATIENT WITH MYOCARDIAL INFARCTION, PULMONARY EMBOLISM AND CORONARY ARTERY PEARL-LIKE LESIONS

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Summary: Our paper presents the case of a patient, aged 34, with a previous anamnesis of three miscarriages and two normal children, transitory Raynaud phenomenon and livedo reticularis with no classical factors for coronary arterial disease, excluding smoking, who was diagnosed with myocardial infarction further complicated by pulmonary embolism. The coronarography and ventriculography findings showed morphological signs of coronaritis, ostial occlusion of LAD, diffuse stenoses of RCA like a string of beads, aneurysm of the anterior wall and apex, ejection fraction of 20%, while echocardiography showed dilatative cardiomyopathy. Elevated IgM anticardiolipin (22 MPLU/mL) antibodies were found at first, and 8 weeks later both IgG (19.8 GPLU/mL) and IgM (15.6 MPLU/mL) were positive. The importance of relatively low levels of anticardiolipin antibody titres was confirmed by a positive anti- β 2 GPI test. All other analyses encompassing investigations of thrombophilia, early atherosclerosis markers including Lp(a), homocysteine, immunological analyses specific for systemic diseases, antibodies against *Borrelia burgdorferi*, HCV, HBV, EBV, were negative. Though the one-year stabilisation of the clinical state and normalisation of acute phase reactants was achieved, along with six-time decrease in sedimentation rate, the disease ended lethally in a sudden death of the patient under home care. In compliance with our surveys, this is the first so far reported case of coexistent pearl-like pattern occurrence in coronary arteries with antiphospholipid syndrome.

Key words: antiphospholipid syndrome, anticardiolipin antibodies, anti- β 2GPI antibodies

Introduction

Antiphospholipid syndrome (APS) is the most frequent acquired thrombophilia accompanied by increased cardiovascular morbidity and mortality, especially in persons under 50 (1, 2). Myocardial

infarction and pulmonary embolism are well-known clinical manifestations of the antiphospholipid syndrome. Positive anticardiolipin antibodies (aCL) were found in 21% of patients under 45 with myocardial infarction (1–3). Increased IgG anticardiolipin antibodies represent an independent risk factor for the occurrence of recurrent episodes following myocardial infarction (1, 4). Certain studies lack firm confirmation of the above-stated hypothesis, mostly due to the fact that elderly patients prevail in the studies conducted, and the short observation period of these studies (1). The aim of the study was to present a unique case of a young patient with APS manifested with serious arterious and venous thromboses, relatively low concentrations of aCL and coexistent pearl-like pattern occurrence in coronary arteries.

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Case report

A housewife, aged 34, felt exhaustion during the first 15 days. After that, the episodes of fleeting dull pains, both in rest and effort, started occurring in her left arm and scapular area of 5/10 intensity degree, the pain being milder in the middle of the chest. Over time, the pain grew more intensive, the episodes longer, sometimes lasting all day and a greater part of the night. Following three weeks, the pain was gradually alleviated, and disappeared completely for a period of one week. Then, abruptly, after carrying out hard field-work, she felt dizziness and nausea and the incessant hours-long pain returned only in the area of the left upper arm and scapula of 8/10 intensity degree, accompanied by sweating, vomiting, weakness and intensive exhaustion. In spite of the diagnosed acute phase of myocardial infarction of the anterior wall based on the first electrocardiogram done, the patient refused hospitalisation. Having spent 2 days at home lying with the above-mentioned difficulties, she was admitted to the district hospital with the signs of subacute myocardial infarction and normal physical findings. Cardiospecific-enzymes were elevated (CK 444 – 167 U/L, CK-MB 62 – 20 U/L, AST 91 – 41 U/L, LDH 981 – 692 U/L). The initial chest roentgenographic findings showed no changes. On the 15th day of hospitalisation she was struck by pain under the left scapula area, dyspnoea with haemoptysis. The electrocardiogram registered typical signs of pulmonary embolism, sinus tachycardia, the shift of QRS axis to the right, with S1Q3T3, and S in V4 – V6. The control chest roentgenography showed pulmonary infarction with Hampton's sign on the right side.

She was then transferred to our hospital to be further examined and treated. The additional careful anamnesis examinations showed that the transitory occurrence of Raynaud's phenomenon and exhaustion were initial symptoms preceding the pain, though Raynaud's phenomenon had also occurred concurrently with the pain in chest and arm over a certain period. Other target anamnestic examinations of connective tissue diseases were negative. The only positive classical coronary disease risk factors were the 10-year smoking of 20 cigarettes per day and the data on the mother's sudden death at the age of 61. She had neither *diabetes mellitus* nor hyperlipidemia. The personal history stated three miscarriages in the periods of 3.5 months (1982), 4.5 months (1983) and 6.5 months (1984) of pregnancy, without any clear gynaecological cause and foetus anomalies. However, in 1984 and 1994, she gave birth to two healthy children. She had used no oral contraceptives or other drugs, or been exposed to toxic factors. The physical examination still was normal, excluding the later occurrence of livedo reticularis, lower heart sounds and weak systolic murmur on the apex. The ultrasound of limb arteries and veins and neck arteries was normal, as well as abdomen ultrasound examination findings. The ocular fundus exa-



Figure 1 The right coronary artery angiogram – long pearl-like stenosis in the mid and distal segment of the artery.

mination found no signs of vasculitis. The electrocardiography confirmed the signs of anterior myocardial cicatrix. The echocardiography showed signs of dilative cardiomyopathy with the left ventricular enlargement EDD 6.3 cm, ESD 5.4 cm, thickening of right ventricular trabeculae. The selective coronarography, ventriculography and pulmonary angiography findings showed ostial occlusion of the left anterior descending artery (LAD), the dominant right coronary artery with diffuse subocclusive pearl-like stenoses of RCA, 70–80% in diameter, behind the acute marginal branch, with slower distal artery filling (TIMI 2 flow). The stated changes morphologically correspond to coronaritis (see *Figure 1*). The proposed myocardial biopsy was rejected. The left ventriculography showed presence of large segmental defects in the left ventricular contractility, the akinetic anterior wall, diskinctic apex and hypokinetic lower wall. Mitral regurgitation of minor degree was found, as well as ejection fraction (EF) of about 20%. The pulmonary angiography showed no pathological changes.

The laboratory analyses disclosed increased acute phase reactants, with the constantly elevated sedimentation (ESR) of about 80–96 mm/h throughout the period longer than a month and a half, and fibrinogen of about 9 g/L. Other routine biochemical analyses were normal, as well as blood counts, including platelet counts and the leukocytes formula. The early arteriosclerosis markers were normal, with cholesterol 5.1 mmol/L, triglycerides 1.8 mmol/L, HDL 1.5 mmol/L, LDL 2.78 mmol/L, Apo A1 1.51 g/L, Apo B 1.44 g/L, Apo B/Apo A1 = 1.26, Lp (a) less than 0.188 g/L, normal homocysteine (10.9 μmol/L). The immunological analyses showed negative results for ANA, ANCA, the rheumatoid factors and antimitochondrial antibodies. Circulating immune complexes were within the referent range as well as immunoglobulins, cryoglobulins, C3, C4 and CH50. The routine haemostatic factors were also normal with INR 1.08, PTT 34.8s. D-dimer was increased amounting to 542 μg/L (its normal value being up to 375 μg/L). However, the IgM aCL were elevated (22 MPLU/mL), as

they also were 8 weeks later (15.6 MPLU/mL). The normal value is up to 10 MPLU/mL. The aCL of IgG class were normal at the first determination, 11.3 GPLU/mL, and slightly elevated 8 weeks later, i.e. 19.8 GPLU/mL (normally up to 19 GPLU/mL). The lupus anticoagulant was negative, as well as VDRL. The antiphospholipid syndrome diagnosis was confirmed by the three positive clinical signs (arterial and venous thrombosis, spontaneous abortions) accompanied by twice repeated elevated anticardiolipin antibodies. The presence of elevated anti beta 2 glycoprotein antibodies ($\beta 2$ GPI) in IgM class 35.6 U/mL (normally less than 20 U/mL) also supported the diagnosis, while the IgG class level of 11.9 U/mL (normally less than 20 U/mL) was within the reference range. The detailed examinations of thrombophilia were normal with antithrombin III 94%, protein C 106%, protein S 99%, activated protein C resistance of 2.13 (2–3.5), euglobulin lysis time, as well as genetic assays of the factor V Leiden and prothrombin 20210. The antibodies to *Borrelia burgdorferi*, HCV, HBV, EBV were negative. The patient was treated with heparin, a high-dosage acenocumarol anticoagulant therapy with target INR 3–3.5, small-dose acetylsalicylic acid, captopril, carvedilol, spironolactone, furosemide, isosorbide mononitrate and predisone. Upon the introduction of predisone administered in the initial doses of 1 mg/kg, the normalisation of acute phase reactants (CRP and fibrinogen) was achieved, along with six-fold decrease in ESR rate, as well as the stabilisation of patient's clinical status. During the further remission period, the patient was treated by azathioprine beside the stated cardiological therapy.

Based on the examinations conducted, the surgical myocardial revascularisation was proposed by the consultation team despite the great operational risk. The patient refused the operation and the previous medication therapy was continued. Although her clinical status stabilisation had been achieved in the duration of 1 year, the disease ended lethally in a sudden death of the patient under home care.

Discussion

Based on the above-mentioned positive clinical and laboratory findings, the diagnosis of antiphospholipid syndrome could be made with certainty. Several studies confirm that elevated anti $\beta 2$ GPI antibodies correlate better with the occurrence of thromboses than the elevated aCL titres, i.e. have higher specificity in the identification of thrombotic risk (1). The same is also confirmed by our patient's laboratory findings where, besides already existing slightly increased aCL titres, positive antibodies to $\beta 2$ GPI were found. It is important to point out that the patient had positive clinical criteria considering the existence of arterial and venous thromboses, as well as spontaneous abortions, along with cutaneous changes in the form of livedo reticularis typically occurring

in APS (5). Livedo reticularis, though not being stated as a main clinical criterion, indicates the necessity of testing such a person to APS. It is absolutely clear that the normal platelet count and aPTT value do not exclude the presence of APS. In case of strong clinical suspicion where classical laboratory tests (LA, aCL, VDRL) are negative, it is recommended that special laboratory parameters of so-called seronegative antiphospholipid syndrome, especially $\beta 2$ GPI antibodies, be analysed (1, 6–10).

Considering the subsequent occurrence of arterial and venous thromboses in our patient, the more detailed analyses to thrombophilia excluded the existence of additional haemostatic disturbance. Also, the target anamnestic, clinical and several-time repeated laboratory immunologic analyses confirmed that there were no signs of coexistent overt underlying systemic diseases. However, the described clinical manifestations still can present merely the first phase of a systemic disease to develop later. Other causes of secondary APS were excluded, along with the drugs administered, infections and other noxes known to induce the production of antiphospholipid antibodies.

The angiographic findings of a beaded pattern or pearl-like changes on the right coronary artery are especially interesting. Such changes are often met in different types of vasculitis, i.e. coronaritis, particularly in polyarteritis nodosa, and somewhat less frequently in the Churg Strauss syndrome (CSS). The typical beaded pattern with focal stenoses and ecstasies has been described in isolated vasculitis of the CNS, but not in case of coronary arteries (11, 12). Some authors report cases of isolated coronary arteritis as a limited variant of the CSS (13). In vasculitis where changes mainly affect large blood vessels as in Takayasu arteritis coronary artery lesions are described in about 10% of the cases. Such lesions are most frequently located in the proximal ostial part of the left anterior descending artery (LAD), which constitutes 72% of all coronary lesions (14). The LAD ostial lesion was present in our patient as well. The diagnosis of coronaritis was supported by an initial increase of the acute phase reactants, being well-known parameters of the disease activity, completely normalised by a corticosteroid therapy.

Stated as differential diagnosis possibilities of similar string-of-beads angiographic changes, apart from coronaritis, there are the antiphospholipid syndrome per se as well as the occurrence of isolated fibromuscular displasia, which is much less frequently found in coronary arteries than renal and other localisations. The fibromuscular displasia findings do not exclude an earlier occurrence of vasculitis, it being known that the same may be one of fibromuscular displasia causes (15). An exact differential diagnosis of the three stated conditions would be histological, but, unfortunately, such an investigation has not been conducted. Even if it had been carried out, the unreliability of vasculitis histological diagnosis would have had to be borne in mind, even in an active

phase of the disease, considering the possibility of skip lesion occurrence (11). Vasculitis is not a characteristic of the primary APS, though occlusive vascular lesions reminding of vasculitis might be described. Acute phase reactants are normal in the primary antiphospholipid syndrome, while they are typically increased in vasculitis or certain forms of the secondary antiphospholipid syndrome (12). Lie (9) states that the phenomena of vasculitis and vasculopathy in the APS are not strictly differentiated, considering that in the APS pathogenesis the thrombosis is a main culprit of vasculopathy, while vasculitis is its consort.

The fourth phenomenon where the pearl-like pattern in coronary arteries may be found is arteriosclerosis. In younger persons without risk factors for arteriosclerosis, which was the case of our patient, the above-mentioned causes of the described pattern are more likely to occur. Therefore, this patient was taken as the case of isolated coronaritis with the secondary antiphospholipid syndrome and, pursuant to the accepted recommendations, treated first by corticosteroids till the acute-phase-reactant normalisation, and then by an azathioprine immunomodulatory therapy maintaining the acute phase reactants within their normal limits along with the achieved clinical remission. The acute phase reactants are considered reliable markers of the process activity and can serve as guides for therapy (11).

The cyclophosphamide therapy was not taken

into account due to the above-mentioned normalised acute phase reactants and toxicity of this drug, but it remained to be considered in case of possible aggravation of disease. During the azathioprine therapy, we took into consideration that this drug induces resistance to the simultaneously administered oral anticoagulants, demanding high dosages to maintain the INR therapeutic range. We were also ready to decrease the dosage of oral anticoagulants in case the azathioprine therapy had to be stopped in order to prevent the possibility of haemorrhagic complications and an abrupt increase of INR.

In spite of reported incidental cases of isolated coronaritis in patients not accompanied by clear electrocardiographic and other clinical signs of the coronary disease development, it happens that young persons, especially females, without classical risk factors for coronary disease, are not taken as serious patients. Even in case of normal initial routine haemostatic tests characteristic for antiphospholipid syndrome, special assays are requested, particularly when, apart from the existent or threatening arterial and/or venous thrombotic incidents, there are other clinical signs as livedo reticularis or miscarriages. The importance of relatively low levels of anticardiolipin antibody titres was confirmed by a positive anti- β_2 GPI test. In compliance with our surveys, this is the first so-far reported case of coexistent pearl-like pattern occurrence in coronary arteries with antiphospholipid syndrome.

ANTIFOSFOLIPIDNI SINDROM U MLADJE BOLESNICE S INFARKTOM MIOKARDA, PLUĆNOM EMBOLIJOM I KORONARNIM LEZIJAMA NALIK NA BROJANICE

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Kratak sadržaj: Prikazujemo bolesnicu staru 34 godine, koja je imala tri spontana abortusa ali i dvoje normalno rođene dece, tranzitorni Raynaudov fenomen, livedo reticularis, bez klasičnih faktora rizika za koronarnu arterijsku bolest, osim pušenja, kod koje je dijagnostikovana akutni infarkt miokarda komplikovan plućnom embolijom. Nalaz koronarografije i ventrikulografije pokazivao je morfološke znake koronaritisa, ostijalnu okluziju prednje leve silazne koronarne arterije, difuzne stenozne desne koronarne arterije, nalik na brojanice, aneurizmu prednjeg zida i apeksa, injekcionu frakciju od 20% (kao i dilatativnu kardiomiopatiju potvrđenu ehokardiografski). Nađeni su povišeni titrovi antikardiolipinskih antitela u IgM klasi (22 MPLU/mL) u prvoj analizi, i u obe klase posle 8 sedmica (aCL IgG 19,8 GPLU/mL i aCL IgM 15,6 MPLU/mL). Značaj pozitivnosti relativno niskih titrova antikardiolipinskih antitela potvrđen je nalazom pozitivnih anti- β_2 GPI antitela. Sve druge analize uključujući ispitivanje na trombofiliju, markere rane ateroskleroze uključujući Lp(a), homocistein, imunološke analize, antitela protiv Borrelie burgdoferi, HCV, HBV, EBV bile su negativne. Posle jedne godine stabilizacije kliničkog stanja i normalizacije reaktanata akutne faze sa šestostrukim padom brzine sedimentacije, bolesnica je naglo umrla na kućnom lečenju. Prema našim pretraživanjima, ovo je prvi objavljeni slučaj udružene pojave lezija nalik na brojanice u koronarnim arterijama i antifosfolipidnog sindroma.

Ključne reči: antifosfolipidni sindrom, antikardiolipinska antitela, anti β_2 GPI antitela

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