CASE REPORT

Atypical clinical manifestation of antiphospholipid syndrome

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KEY WORDS

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ABSTRACT

Antiphospholipid syndrome is a disorder characterized by recurrent venous or arterial thrombosis and/or recurrent abortions associated with persistently elevated levels of antiphospholipid antibodies. In some patients antiphospholipid syndrome occurs in association with systemic lupus erythematosus, or other autoimmune disorders or malignancies. Antiphospholipid syndrome can be induced by certain drugs. A correct diagnosis of this disease is necessary as it is potentially associated with serious and sometimes life-threatening complications. Clinical presentations of antiphospholipid syndrome may vary widely even in the same patient. The time between individual manifestations of the disease also varies considerably. Therefore its early detection requires a strong index of suspicion especially when thrombosis occurs at unusual sites or non-specific symptoms predominate in the clinical presentation. We report a case of a 20-year-old woman with a recent history of pulmonary embolism who was admitted to the hospital because of severe symptomatic anemia. Once the diagnosis of antiphospholipid syndrome coexisting with systemic lupus erythematosus as a primary disorder has been established, implemention of specific treatment resulted in markedly improved condition.

INTRODUCTION Antiphospholipid syndrome is a disorder characterized by recurrent venous or arterial thrombosis and/or abortions, associated with persistently elevated levels of antiphospholipid antibodies against cardiolipin, phosphatidylserine or other proteins (especially β_2-glikoprotein I) and/or lupus anticoagulant.[1] In some patients antiphospholipid syndrome occurs in association with other diseases, e.g. systemic lupus erythematosus (SLE), or, rarely, with other autoimmune disorders or malignancies and during HIV infection or treatment with certain drugs (dihydralazine, chinidine, chlorpromazine).[2-4] It is estimated that SLE is observed in 30–40% of patients with antiphospholipid syndrome, while only 10% of SLE patients suffer from antiphospholipid syndrome.[2,5] The risk related with misdiagnosis of antiphospholipid syndrome makes it obligatory to perform diagnostics in all patients, in whom the presence of even 1 of the main clinical symptoms is observed.[1,3] The clinical case presented in this paper shows that the course of antiphospholipid syndrome can be atypical and in such a situation diagnosis poses a difficult diagnostic challenge.

CASE REPORT A 20-year-old female patient was urgently admitted to the hospital to establish the causes of and implement treatment of severe anemia. 18 days earlier she was hospitalized in another ward of the Department of Internal Medicine because of overt severe right-ventricular insufficiency. The computed tomography (CT) showed the presence of huge thrombotic material within the right lower lobe artery with bilateral pleural exudation. Echocardiography revealed moderate tricuspid regurgitation (Vmax of regurgitation wave to 4 m/s), right atrium area 21 cm^2, tricuspid insufficiency area 10 cm2 and elevated right ventricular systolic pressure (70 mmHg). On color *Doppler duplex* sonography thrombosis in veins of lower extremities and minor pelvis was not observed. Taking into consideration the CT examination, features of acute right ventricular insufficiency shown by the echocardiographic examination, the severe general state and

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developing respiratory failure, the decision to implement fibrinolytic treatment with streptokinase (intravenous infusion of 1.5 million units within 2 h) was made. Treatment was continued by administration of low-molecular-weight heparin, and oral anticoagulant in ambulatory conditions. At the time moderate anemia (hemoglobin [Hb] – 6.39 mmol/l, erythrocytes, 3.34 T/l, hematocrit [Ht] – 0.29 l/l) was observed, while platelet and leucocyte counts were within the normal ranges.The observed anemia was diagnosed de novo, as it was not found 2 weeks prior to t hospital admission during routine tests, recommended by the general practitioner due to planned employment. On admission severe anemia (Hb-4.59 mmol/l, erythrocyte count 2.44 T/l, Ht – 0.2 l/l, mean corpuscular volume – 82.0 fl, mean corpuscular hemoglobin – 30.3 pg, mean corpuscular hemoglobin concentration – 37.0 g/dl), normal leukocytosis (5.67 G/l) and a slight decrease in platelet count (109 G/l) in laboratory tests were found. Beside increased International Normalized Ratio (INR), as a result of implemented treatment, insignificantly prolonged kaolin cephalin clotting time was observed (values from 37.5 to 43.7 s, with a normal range of 29–40.2 s). Because of a history of pulmonary embolism and dyspnea on admission, scintigraphy was performed, showing the presence of multiple small perfusion defects within segments 1, 2, 6, 8 and 9 of both lungs. After modification of antithrombotic treatment (temporary administration of low-molecular-weight heparin instead of vitamin K antagonist) and peripheral blood sampling for specific hematological tests and bone marrow aspiration, with regard to the severe general state of the patient (drowsiness, weakness, dyspnea, exercise intolerance, tinnitus, palor of the skin and mucous membranes – with no evident symptoms of bleeding) 2 units of erythrocyte mass were transfused, obtaining an increase in the Hb level of 6.95 mmol/l, erythrocytes to 3.78 T/l and Ht to 0.315 l/l. Awaiting empirical results, preparations of folic acid, iron and vitamin B12 were also administered, but the last 2 preparations were discontinuated after 3 days because the increased level of iron (44.9 μmol/l, norm to 32.2 μmol/l) and the normal vitamin B12 level (367 pg/ml, norm: 189–883) were observed. In laboratory tests the following abnormalities were detected: significantly increased reticulocytosis (0.058 l/l), mild hyperbilirubinemia (32.5 μmol/l, norm to 20), positive indirect antiglobulin test, normal bone marrow cellularity with features of normoblastic regeneration, decreased haptoglobin level (0.07 g/l, norm: 0.3–2.0), presence of schistocytes in smear, and increased D-dimer level (1145 μg/l, norm to 130). The results of tests for paroxysmal nocturnal hemoglobinuria (Ham and sucrose hemolysis tests) were negative. Antithrombin, proteins C and S levels measured to exclude trombophilia (blood was taken during therapy with a low-molecular-weight heparin) were within the reference range. Despite red blood cells transfusion, a constant progression of anemia accompanied by a continuous decrease in platelet count (to 49 GPL on the 10th hospital day) was observed. Progressing anemia and results of performed tests justified administration of glucocorticoids (or other immunosuppressive drugs), however at first the patient refused. With regard to the presence of significant clinical symptoms of anemia on the 7th and 10th hospital days subsequent transfusions had to be performed. Periodic increase in body temperature (to 40°0) observed from the very beginning of hospitalization, unknown etiology (diagnostics in progress) and the patient's history (bacterial endocarditis at the age of 8 years), forced the implementation of empirical antibiotic therapy before the culture results were obtained (in which the presence of bacteria and fungi in blood, urine and in material collected from the nasal cavity, throat and tonsils was not eventually confirmed, and the valve vegetations were not detected). However, neither initial administration of ceftazidime with amikacin, nor subsequent administration of meropenem and antifungal itraconazole did nor normalize body temperature. Febrile states did not seem to result from viral infection, as negative results of infection with Epstein-Barr, cytomegaly, type A, B and C hepatitis, herpes and HIV virus were obtained. The positive result of anticardiolipin antibodies in IgG (66.5 GPL, norm to 20) and IgM class (12.5 MPL, norm to 10.0) obtained 10 days after admission and pulmonary embolism in the patient's history suggested the diagnosis of antiphospholipid syndrome and justified continued therapy with acenocoumarol. However, the presence of insignificantly positive result of the HEp-2 test, the presence of antibodies against native DNA in the qualitative test with indirect immunofluorescence, and a decreased level of C4 complement component in relation to the clinical picture, especially febrile states and pleural effusion, raised the suspicion that the syndrome could be related to connective tissue disease, most probably SLE. Thus it was possible to convince the patient about the validity of therapy with glucocorticoids and implementation of prednisone in an initial daily dose of 1 mg/kg of body mass. Considering the presence of febrile states with concomitant significant weakness and features of pleural involvement, the decision was made to administer chloroquine initially in a daily dose of 500 mg for 7 days, and then in a maintaining dose of 250 mg. The therapy led to the quick clinical improvement, regression of febrile states, pleural involvement and the improvement in hematological parameters, especially platelet count. The further successive improvement in values of the hematological parameters was observed, and after 3 months of the treatment only mild hemolysis (reticulocytosis, 0.017/l, bilirubin level, 22.2 μmol/l) and increased (as a side effect of acenocoumarol intake) INR values were found. Blood cell counts (including platelets) were normal. After 2 months

after discharge, the patient observed transient exanthema, resulting from sun exposure, and painless ulcerations within the oral cavity. These symptoms, previously not observed, ceased after increasing the prednisone dose. Control immunological tests, performed 4 months after the hospitalization showed the presence of antinuclear antibodies at a titer of 1:640 (confirmed by the Immunoblot test) showing a homogenic and granular pattern, and against neutrophil cytoplasm antibodies, the increased γ-globulin level, and the decreased level of C4 complement component. The result of anticardiolipin antibodies was persistently positive. Anti-SSA, anti-SSB, anti-Jo-1, anti-PM-Scl, anti-Scl-70 and anti-nRNP antibodies were not found. Pleural effusion,, the presence of ulcerations in the oral cavity, characteristic hematological and immunological abnormalities and the presence of antinuclear antibodies enabled the unambiguous diagnosis of SLE on the basis of the American College of Rheumatology criteria. Presently, the patient is in a good general state, and has not reported any subjective symptoms. She is treated with prednisone (15 mg/day), chloroquine (250 mg/day) and an acenocoumarol dose which enables the INR value to be maintained at around 3.0.[1]

DISCUSSION Although in the case of typical clinical picture the diagnosis of antiphospholipid syndrome is easy to make, in some patients with an atypical course, diagnosis is an important diagnostic challenge.[1,4] Misdiagnosis of the disease may have adverse outcomes,[2,3] while – as the example of the current patient confirms – etiology establishment and implementation of appropriate treatment can result in a significant improvement in the clinical state.

Pulmonary embolism was the initial disease/symptom, which led to patient hospitalization. Pulmonary embolism is one of the possible manifestations of antiphospholipid syndrome, and in particular cases may lead to the development of pulmonary hypertension and isolated tricuspid insufficiency.[6] Although in the course of this syndrome pulmonary embolism is commonly observed, it usually concerns patients with symptoms of venous thrombosis or a history of recurrent abortions and usually occurs in the form of multiple emboli in small pulmonary vessels.[7] Contrary to these typical cases, pulmonary embolism in the current patient was an initial clinical symptom. However, coexistence of lesions in small pulmonary vessels could not be eliminated and was confirmed by the severe clinical state of the patient on admission and the results of perfusion scintigraphy performed over 2 weeks after the embolism, which revealed the presence of multiple small uptake defects within both lungs. A marker, which could be a predictor of the risk of pulmonary embolism in the course of the above clinical unit, is unavailable at the present moment. Some authors attribute such a role to kaolin cephalin time.[8] In the repeated tests the time was close to the upper limit of the reference range or exceeded it insignificantly. Although generalization on the basis of evaluation of a single patient is loaded with the risk of mistake, the described case speaks against the role of kaolin cephalin time as a marker for determining risk of pulmonary embolism. In the present case it was also observed that pulmonary embolism occurred despite a moderately increased level of antiphospholipid antibodies. This observation is in line with the results of large clinical studies conducted in 2370 patients, in which there was no correlation between the level of these antibodies and the risk of pulmonary embolism.[8] It should be assumed that certain, not established so far subgroups of antiphospholipid antibodies play a causative role in this complication. It is interesting that in the discussed patient symptoms of pulmonary embolism were not associated with evident venous thrombosis of lower extremities and lower abdomen. Indeed, on this basis it cannot be assumed, that these vessels are a source of thrombotic material. However, it does not exclude the pulmonary artery as the primary source of embolus. Even though in available data a high, up to 80%, percentage of thrombosis recurrence in the course of antiphospholipid syndrome is stressed, in the described patient during a 1.5-year long observation episodes of embolism were not reported.[7] This is an argument showing that oral anticoagulant in combination with specific treatment of lupus is an effective preventive treatment for pulmonary embolism developing on the basis of antiphospholipid syndrome coexisting with SLE.

The second crucial symptom in the described patient was severe anemia, which periodically required transfusion of erythrocyte mass. Its relation with the basic disease was evident, and was confirmed by the absence of anemia in the routine laboratory test performed 2 weeks prior to the episode of pulmonary embolism. Moreover, its regression was observed following coadministration of acenocoumarol, prednisone and chloroquine, when other drugs (iron salts, folic acid and vitamin B_{12}) did not produce any improvement, and blood transfusion resulted only in a transient improvement. A decreased haptoglobin level, thrombocytopenia and cell regeneration in bone marrow biopsy indicated a hemolytic anemia. The assumption was made that it was probably associated with microangiopathy, which was confirmed by gradually lower thrombocytopenia, persistently increased D-dimer levels and the presence of schistocytes in peripheral blood. On the other hand, the positive result of the indirect antiglobulin test indicateed immunologic mechanisms in the pathogenic mechanism of anemia. Hemolytic anemia is commonly described in the current literature in antiphospholipid syndrome; however, with the exception of very uncommon fulminant cases, it was not diagnosed immediately and was not as dramatic as observed in our patient.[9,10]

Concominant transient increase in body temperature led to administration of empirical antibiotic therapy, unfortunately with no expected improvement, which in our opinion was another argument for an autoimmune cause of the observed clinical manifestations.

Pulmonary embolism coexisting with severe anemia, which is not a side effect of fibrinolytic treatment, is infrequently observed. It should always arouse the suspicion of thalassemia, sickle cell disease and paroxysmal nocturnal hemoglobinuria, as in these disorders – thalassemia in particular – an iron level can be increased.[11,12] However,a negative family history, lack of developmental anomalies typical of this disorder (facial dysmorphism similar to that in Down syndrome, metaphyseal hypertrophy, hepato- and splenomegaly, cardiac hypertrophy, brown skin) and no evidence of microcytosis in our patient spoke against thalassemia. Sickle-cell anemia was excluded on the basis of a negative family history, the presence of spleen, ethnicity, and a negative result of the sickle cell test. On the other hand, the absence of hemoglobinuria and clinical symptoms of hemolytic crisis (nocturnal in particular) and the negative result of Ham and sucrose tests spoke against paroxysmal nocturnal hemoglobinuria.The described case, according to available data, is the first in which pulmonary embolism and severe anemia in antiphospholipid syndrome in SLE patients coexist. Currently we are not able to explain such a dramatic course of pulmonary embolism and anemia. Although severe clinical presentation is characteristic of the so-called catastrophic antiphospholipid syndrome, no microvascular abnormalities in 3 different locations required for such diagnosis refutes this hypothesis.[1,3]

Despite a suggestive clinical picture at the time of establishing diagnosis of antiphospholipid syndrome, the patient did not fulfil the definitive criteria of SLE and in consequence the diagnosis was unambiguously confirmed only after several months.[5] Although it is assumed that every case of antiphospholipid syndrome requires evaluation to confirm or exclude coexistence of systemic disease, the present case proves that in unclear cases the patient should be carefully followed and undergo repeated immunologic tests after several months.

The current case speaks for the necessity of considering differential diagnosis of SLE-related antiphospholipid syndrome, especially if pulmonary embolism without thrombotic risk factors coexists with anemia of unknown origin. Implementation of oral anticoagulation and oral glucocorticosteroids with chloroquine may prevent pulmonary embolism and anemia recurrence, and result in subsiding signs and symptoms.

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