

A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATODES, HIGH pANCA ANTIBODIES AND END-STAGE RENAL FAILURE

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Abstract. A 47-year-old female patient with active Systemic lupus erythematosus (SLE) – skin, joint, hematological, and renal involvement, was admitted due to rapidly progressive renal failure at the background of very high anti-dsDNA and pANCA antibodies. Active pathogenetic treatment was started – pulse therapy with methylprednisolone, intravenous immunoglobulins (IVIG) and cyclophosphamide, blood transfusions were performed, symptomatic treatment with infusions ad diuretic was initiated. Due to progression of renal failure with volume overload and increase in urea and creatinine levels renal-replacement therapy was initiated. The patient developed *E. faecalis* and *E. durans* sepsis with disseminated intravascular coagulation and ground-glass-type lung changes and the condition further deteriorated to fatal multiorgan failure. The authors discuss the role of pANCA antibodies in SLE with renal and lung involvement.

Key words: systemic lupus erythematosus, lung and renal involvement, pANCA, sepsis

INTRODUCTION

Systemic lupus erythematosus is a systemic connective tissue disease in which mainly antinuclear (ANA) and antiphospholipid antibodies (APLA) cross-react with the skin and the internal organs and cause different clinical symptoms. The incidence of SLE is 15-48/100,000, affecting more often females and showing preponderance towards the African race. The disease rarely starts before puberty or after the age of 60 years. Women are affected 7-10 times more frequently than men [1]. The renal and lung involvement, vasculitis and septic complications, along with the secondary antiphospholipid syndrome, are among the most severe disease manifestations, often determining the prognosis of the patient.

CASE PRESENTATION

We present a 47-years-old female patient admitted due to diffuse edema on the legs progressing over the past two months, decreased urine output to 100-200 ml/24 h, joint pains in the hands, oral aphthosis, and fatigue. The clinical-laboratory investigations two months before the admission revealed mild renal failure – serum creatinine of 180 µmol/l, positive protein on dip-stick urine examination and negative APLA.

The patient has had 18-year history of SLE – skin, joint, hematological involvement. At the admission she was on treatment with methylprednisolone

8 mg/day and chloroquine 250 mg/day. She had been treated with methylprednisolone and intravenous immunoglobulin (IVIG) pulses. In 2015 she had septic arthritis of the right radiocarpal joint. In 2014 balloon angioplasty of the right popliteal artery for stenosis and amputation of the 5-th toe of the right foot was performed. She was diagnosed with Burger's disease and was given pentoxifylline and oral anticoagulant (apixaban). In 2007 the patient underwent laparohysterectomy for carcinoma coli uteri. The patient was an ex-smoker.

At the admission the patient was in impaired general condition, with normal body temperature, rhonchi in the right lung base. Rhythmic heartbeat and systolic murmur 2/6 on the precordium were recorded. Liver was palpable at the costal rim. Marked edema on the lower extremities was present. Jaccoud-type deformities on the hands were found.

The clinical-laboratory investigations at the admission revealed negative rapid antigenic test for SARS-CoV-2, severe anemia (hemoglobin 67 g/l), normal white blood cell (7.36 G/l) and platelet (358 g/l) count, increased inflammatory markers (ESR 75 mm/h, CRP 17.6 mg/l), low total protein (60.9 g/l) and albumin (22.4 g/l), high serum creatinine (453 µmol/l) and potassium (6.1 mmol/l), proteinuria of 2.76 g/l, low estimated GFR of 9.7 ml/min (MDRD). The immunological investigations revealed high-positive anti-dsDNA screen > 200, low C3 and

C4 levels, high pANCA>1:1280, negative anti-PR3 and anti-MPO, negative Quantiferon test.

The chest X-ray investigation showed opaque right lung base and pleuro-diaphragmatic adhesions (Figure 1). The X-ray investigation of the hands revealed ankylosis of the radio-carpal, carpal and carpo-metacarpal joints of the right hand with luxation of several metacarpophalangeal and interphalangeal joints (Figure 2).

The chest computed tomography scan (CT) showed diffuse edema of the subcutaneous fat tissue, bilateral pleural effusions (more pronounced to the right), diffuse ground-glass-type parenchymal lung changes and adhesions in the right lung base (Figure 3).

Abdominal ultrasound investigation presented both kidneys normal in size with increased parenchymal echogenicity, marked liver congestion, ascites, liver hemangioma. The transthoracic echocardi-

ography showed no vegetations and revealed mitral valve regurgitation III grade, aortic valve regurgitation II grade, tricuspid valve regurgitation III grade, EF 30%, small pericardial effusion of 70 ml.

The patient received hemotransfusions of red-blood-cell concentrates, 3 intravenous infusions of methylprednisolone 1000 mg in three consecutive days, intravenous pulse with cyclophosphamide 500 mg, IVIG (overall 90 ampoules), Human albumin, infusions, diuretics, low-molecular weight heparin (Fraxiparine 0.4 ml/day). Hemoglobin levels reached 91 g/l, ESR and CRP levels decreased to normal levels but due to progression of renal failure with serum urea levels reaching extremely high levels (49 mmol/l) with persisting volume overload the patient was started on hemodialysis.

The patient developed one episode of hematemesis and underwent fibrogastroscopy reveal-



Fig. 1. Baseline chest X-ray investigation – opaque right lung base and pleuro-diaphragmatic adhesions



Fig. 2. Baseline X-ray investigation of both hands – ankylosis of the radio-carpal, carpal and carpo-metacarpal joints of the right hand with luxation of metacarpophalangeal and interphalangeal joints

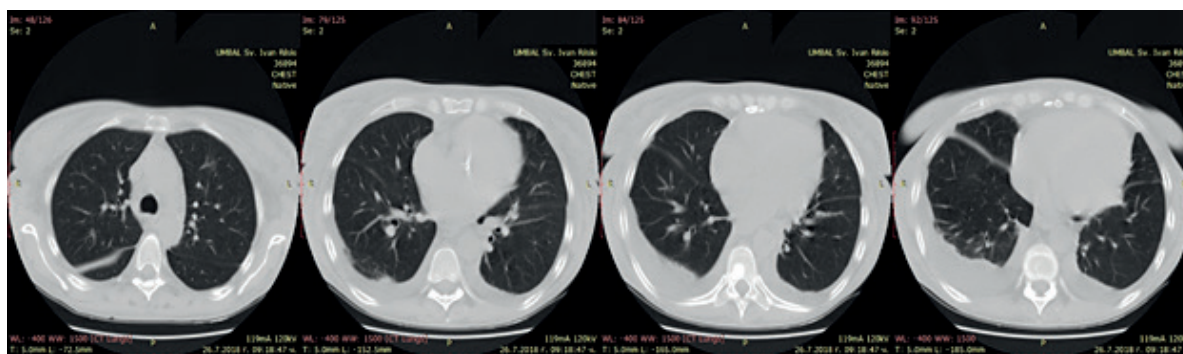


Fig. 3. Baseline chest CT – diffuse edema of the subcutaneous fat tissue, bilateral pleural effusions (more pronounced to the right), diffuse ground-glass-type parenchymal lung changes and adhesions in the right lung base

ing candida-associated esophagitis, hiatus hernia and chronic gastritis. The patient received another hemotransfusion with methylprednisolone pulse (1 g), antibiotic (ceftriaxone 1 g/day) and antimycotic.

The patient gradually developed progressive peripheral cyanosis and an enlarging hematoma on the median surface of the left thigh at the puncture site of the central venous access for dialysis and on the pubic area. The control investigations registered leukocytosis (18 G/l) with low lymphocytes (2.4%) and neutrophilia (95.6%), mild anemia (hemoglobin 102 g/l), low platelet count (75 G/l), hypoalbuminemia and hypoproteinemia, increased liver enzymes (ASAT 193.1 U/l, ALAT 411.5 U/l, GGT 335 U/l) with negative HBs antigen and anti-HCV and anti-HAV antibodies, increased d-dimer (625 ng/ml, normal levels < 255), decrease in fibrinogen (1.93 g/l), prolongation of aPTT (the blood not coagulating), PT 23.4".

During the next two days the administration of antibiotic, antimycotic, low-molecular weight heparin was stopped and heparin-free dialysis was performed, fresh-frozen plasma and platelet concentrate were transfused. Despite the therapeutic efforts platelets fell to 8 G/l, d-dimer increased to 5535, fibrinogen fell to 0.85, PT elongated to 32.8", aPTT remained prolonged (37"), liver enzymes increased further (ASAT – 2008; ALAT – 1850; LDH – 12297; GGT – 440 U/l). Alkaline base balance showed marked disturbances: pH – 7.35; $p\text{CO}_2$ – 3.54 kPa; $p\text{O}_2$ – 6.7 kPa; BEecf – 11.2 mmol/l; SBC – 16.9 mmol/l; satO_2 – 84%.

The patient was transferred to Intensive care unit and remained on intravenous methylprednisolone 80 mg/day, ceftriaxone and low-molecular weight heparin (Fraxiparine 0.4 ml/day). Enterococcus durans was isolated from the urine and E. faecalis – from hemoculture, and ceftriaxone was replaced with ampicillin/sulbactam 1.5 g/day. The control chest X-ray revealed decreased translucency of the right lower lobe, uneven right diaphragmatic dome and hypoventilation changes (Figure 4).

The patient was put on oxygen (4-10 l/min), methylprednisolone 100 mg/day, ampicillin/sulbactam 1.5 g/day, apheretic platelets, fresh-frozen plasma, erythropoietin-alpha 2000 IU/48 h, Fraxiparine 0.4 ml b.i.d., daily hemodialysis sessions. The patient developed gangrenes of the fingers and toes, gingivorrhagia and thrombosis of the central venous access. Marked deterioration of the hematology parameters was noted: leukocytes 1.37 G/l, hemoglobin 77 g/l, platelet count 24 G/l, creatinine 283 $\mu\text{mol/l}$ with urea 35.09 mmol/l, potassium 4.32 mmol/l, ASAT – 46.59 U/l; ALAT – 65.83 U/l; CRP – 63.07 mg/l.



Fig. 4. Control chest X-ray – decreased translucency of the right lower lobe, uneven right diaphragmatic dome and hypoventilation changes

Despite the pathogenic and symptomatic treatment the patient developed polyorgan failure and deceased.

DIFFERENTIAL DIAGNOSIS AND THE ROLE OF PANCA IN SLE

The differential diagnosis of SLE with ANCA-associated lung and kidney vasculitis and secondary coagulation abnormalities (in relation to vasculitis, hematoma and infection) in this patient includes disseminated intravascular coagulation of other origin with low platelet count, prolonged PT and aPTT, high d-dimer and both bleeding and thrombosis; the high LDH could be associated with the hematoma and/or with ANCA-associated small-vessel vasculitis with microhemolysis. Another possible differential diagnosis is the thrombotic microangiopathy, characterized with low platelet count, systemic microvascular thrombosis without bleeding, normal PT and aPTT, mild increase in d-dimer and increased schizocyte number in peripheral blood (5-10%). Another differential diagnosis is the type 1 and type 2 heparin-induced thrombocytopenia. In type 1 there is low platelet count due to anti-platelet antibodies and bleeding, and in type 2 – activating anti-platelet antibodies with microthrombosis and/or increase of the primary thrombus and low platelet count without bleeding tendency. PT and aPTT are normal in both types and d-dimer could be slightly increased. Last but not least is the catastrophic antiphospholipid syndrome that manifests with the development of multiple organ thromboses and dysfunction with low or normal platelet count, normal PT, normal or prolonged aPTT (lupus anticoagulant) and mild increase in D-dimer.

In our patient the most probable mechanisms in the development of disseminated intravascular coagulation that lead to multiorgan failure and death are a combination of active severe systemic (sepsis) enterococcal infection (with two types of enterococci – *E. faecalis* and *E. durans*) [2], vascular damage due to pANCA [3] (including lung and renal involvement and peripheral gangrenes) and large hematoma inducing coagulation disturbances [4].

THE ROLE OF HIGH PANCA IN LUPUS NEPHRITIS

Perinuclear ANCA are detected with indirect immunofluorescence technique in up to 20% of SLE patients. They are found more frequently in lupus nephritis (LN) patients with high dsDNA antibodies and are associated with the presence of class IV (diffuse proliferative) LN. LN patients with positive pANCA show faster progression to renal failure [5, 6]. Moreover, pANCA-associated necrotizing rapidly progressive glomerulonephritis could superimpose upon LN in pANCA-positive SLE patients. Renal biopsies of such patients reveal necrotizing glomerulonephritis with fibrinoid necrosis and glomerular basal membrane rupture, intra- and extracapillary deposition of fibrin, oligoimmune glomerular immune depositions. These cases are interpreted as ANCA-associated necrotizing and crescentic glomerulonephritis in LN [7]. ANCA are also known to cause endothelial

damage and induce thrombosis [3]. Unfortunately, no renal biopsy was performed in our patient due to severely impaired general condition.

In conclusion, we present a patient with high SLE activity, positive pANCA and signs of disseminated intravascular coagulation at the background of enterococcal sepsis, large hematoma and vasculitis. Despite the adequate treatment the patient developed multiorgan failure and deceased.

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