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CASE REPORT

Thrombosis of the lower right limb in an 11-year-old boy – the first manifestation of systemic lupus erythematosus triggered by SARS-CoV-2 infection

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ABSTRACT

The case report describes an 11-year old boy with sudden onset lower right limb thrombosis, hypertension and nephritic syndrome. Laboratory findings revealed positive results of anti-ANA, anti-dsDNA, lupus anticoagulant and COVID-19 IgG antibodies. Vascular ultrasound and computed tomography detected active thrombosis of the right popliteal vein. Kidney biopsy confirmed fourth class lupus nephritis. The patient responded well to a combination of steroids, cyclophosphamide, hydroxychloroquine, rituximab, alteplase, heparin and amlodipine, with the resolution of thrombosis and nephritic syndrome, stabilization of blood pressure and improvement in laboratory findings. The case highlights the importance of prompt diagnosis and appropriate treatment of systematic lupus erythematosus with vein thrombosis and lupus nephritis in children, particularly in male patients. Overall, this case emphasizes the possibility of virus triggering factors in systematic lupus erythematosus and the importance of regular check-ups, monitoring of symptoms in preventing complications and improving the long-term outlook for patients with systemic lupus erythematosus.

KEY WORDS:
thrombosis, SLE, COVID-19, SARS-CoV-2.

INTRODUCTION

Systematic lupus erythematosus (SLE) is a rare autoimmune disease that can affect any part of the body, including the skin, joints and internal organs such as the heart, lungs and kidney [1]. Considering renal changes in SLE, the importance of lupus anticoagulant (LA) and its possible correlation with antiphospholipid syndrome (APS) cannot be omitted. Antiphospholipid syndrome is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies. The Sydney Classification Criteria for Definite Antiphospholipid Syndrome are met when at least one clinical criterion (thrombosis or pregnancy morbidity) and one laboratory criterion (LA, anticardiolipin antibodies or a β2-glycoprotein I antibodies) are present. The epidemiology of APS in the general population is poorly understood and in different studies the frequency varies between 1 and 2 cases *per* 100,000 and 40 and 50 cases *per* 100,000. Clinical manifestations may include thrombosis, thrombocytopenia, bleeding, fetal loss, livedo reticularis and neurological complications. Additionally, it is well documented that viral infections are an environmental factor that contributes to the development of autoimmunity. In terms of pathophysiology, COVID-19 as a new entity is believed to cause a dysregulated cytokine response which could potentially be exacerbated by the shift in Th1 to Th2 response seen in SLE. Moreover, it is possible that SARS-CoV-2, as occurs with

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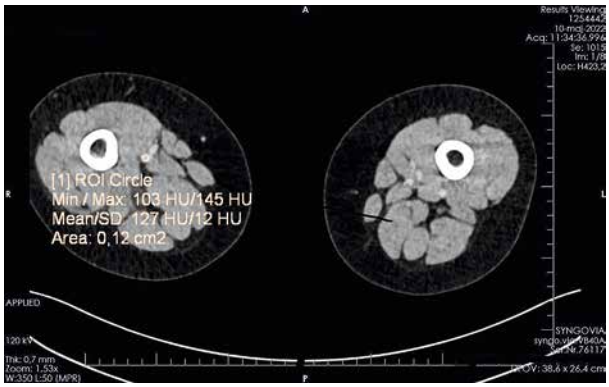

FIGURE 1. Patients' origins

other viruses, might lead to the formation of antiphospholipid antibodies, potentially contributing to the increased rates of thrombosis seen in COVID-19.

SLE can present at any age, but it is less common in children. In about 10–15% of all cases onset occurs during childhood and adolescence, usually presenting after the age of 10 years. The disease is more common in the female than male population although in childhood and adolescence more males are affected than in adult-onset cases. The female-to-male ratio is 4.5 : 1 through childhood and adolescence. In male patients, the younger the age at the time of SLE diagnosis, the more severe the course [2, 3] of the disease tends to be. Therefore, early diagnosis and appropriate management are crucial in ensuring the best possible outcome for the patient.

CASE REPORT

An 11-year-old male patient was admitted to the Pediatric Nephrology Department of Poznan University of Medical Sciences with sudden pain and edema of the right lower limb, tachycardia, and hypertension. Two days before admission, due to stomach pain, a urine test was performed, showing proteinuria and erythrocyturia. On admission, the patient had presented a tough, painful right shin with a 3 cm length circuit compared to the left. Laboratory findings showed hemoglobin 10.5 g/dl, white blood count 8.990/mm^3, platelets 78,000/µl, BUN 40 mg/dl, creatinine 0.77 mg/dl, INR 1.4, prothrombin time 71%, fibrinogen 404 mg/dl, activated partial thromboplastin time 71.5 s, D-dimer 6470 mg/l (N < 500), cystatin C 1.43 mg/l (N: 0.53–1.01), ALAT 23 U/l, ASPAT 22 U/l, hsTnI 249 ng/l, BNP 160.4 pg/ml (N < 100), ANA 1 : 2560, anti-ds-DNA positive, OB 55 mm/h. The urine sample showed protein 3900 mg/dl, erythrocytes 10–15/hpf. C3 and C4 components were within the normal range. Serological tests for anti-EBV, HCV influenza and HbsAg were negative. Anti-CMV IgG was positive. COVID-19 IgG antibodies were positive with a titer of 52.42. The patient was not vaccinated against SARS-CoV-2, and four weeks before admission to the hospital he had infection with fever and general weakness which was not confirmed by nasopharyngeal swab molecular tests. The activity levels of C protein and free S protein, V, VII coagulation factors were within the normal range whereas VIII coagulation factor activity was lower than normal. A1298C, G1691A, and G20210A mutations were tested and not found. Lupus anticoagulant was strongly positive. Vascular ultrasound on admission showed active thrombosis of the right popliteal vein, which was confirmed on CT (Fig. 1). Abdomen ultrasound revealed increased renal parenchymal echogenicity, features of liver, and pancreas steatosis. Kidney biopsy demonstrated numerous active and chronic inflammatory changes with more than half of the glomeruli in the kidney biopsy having lesions or scarring; the result was compatible with fourth-class lupus nephritis by EULAR criteria. The patient was also examined by a rheumatologist and ophthalmologist, without finding any vascular changes on the fundus. In the echocardiogram, trace amounts of pericardial fluid were found, and based on the cardiologist's examination, bed rest was advised. Based on clinical and laboratory findings, the patient was diagnosed with SLE. Treatment [4] was based on steroids [5] (orally prednisone 2 mg/kg for 14 days and next 3 intravenous pulses of methylprednisolone 15 mg/kg), then 3 doses of cyclophosphamide (500 mg/m^2) administered over 3 months with hydroxychloroquine (2 mg/kg), and after 6 months rituximab (725 mg/m^2) was administered. Due to thrombosis and elevated blood pressure, alteplase (0.9 mg/kg, 10% of drug administered as a bolus then 90% of solution as a slow injection over an hour), heparin (continuous flow injection of heparin over first 12 hours – 10000 IU/4 hours, then enoxaparin 1 mg/kg twice *per* day), and amlodipine were also added to the treatment. Temporarily, the patient needed dihydralazine (1 mg/kg/min) in continuous infusion. Ultrasound and angio-CT examinations showed patency of the right popliteal vein after 2 weeks of treatment, and blood pressure and heart rate were also stabilized. After 6 weeks of treatment, ANA antibodies were 1 : 1280, and after 12 weeks of treatment, LA was confirmed positive. Currently, the patient does not require hospital treatment and is under the supervision of a nephrologist with orally admitted steroids and hydroxychloroquine.

DISCUSSION

The diagnosis of SLE in an 11-year-old boy was based on the clinical and laboratory findings, including positive ANA and anti-dsDNA antibodies, and LA positivity and thrombocytopenia. Fourth class lupus nephritis [6] was confirmed by kidney biopsy with presence of active renal lesions and scarring within more than half of the glomeruli. Lupus nephritis is a common constituent of SLE and affects 40–80% of pediatric patients. The main clinical manifestations are haematuria and nephritic syndrome (NS). Our patient presented a benign course of NS di-

agnosed mainly in laboratory tests during admission to the hospital without generalized edema. Considering renal changes in SLE, the importance of LA and its possible correlation with APS should be considered [7]. Clinical manifestations of APS may include thrombosis, thrombocytopenia, bleeding, fetal loses, livedo reticularis and neurological complications. As stated in the literature, while thrombotic events rarely occur, a higher proportion of this complication is related to antiphospholipid antibody positivity in children and adolescents compared to adults [8]. However, in our patient lower limb thrombosis was a leading reason for the patient to contact healthcare providers.

Presence of LA is associated with greater risk of thrombosis, and, as studies show, steroid therapy might reduce its activity but it does not cause its disappearance [9]. Rare events such as deep vein thrombosis and pulmonary embolism might occur. Therapies such as anticoagulants and thrombolytics are used in pediatric patients, but management decisions for children are directly deduced from recommendations for adults [10].

It is noteworthy that our patient, who was not vaccinated against SARS-CoV-2, was positive with COVID-19 IgG antibodies at a titer of 52.42. A previous infection in the boy with fever and general weakness was not confirmed by molecular tests and preceded the first symptoms of SLE. Autoimmune and autoinflammatory disorders can by induced by various viral infections with many immunological stimuli. It is possible that SARS-CoV-2 could stimulate the formation of immune complexes and the development of lupus nephritis and LA. The mechanism of the wide range of COVID-19 immunologic manifestations remains unclear, and could be explained by autoreactivity, autoimmunity, or a mixed pattern physiology [11]. The age and sex of our patient signal a rare and aggressive clinical course of SLE with positive LAC and vein thrombosis as the main clinical manifestations. The patient was started on intensive combination therapy of steroids, cyclophosphamide, hydroxychloroquine, and rituximab [12, 13]. Alteplase, heparin, and amlodipine were added due to thrombosis and elevated blood pressure. The patient responded well to treatment, as evidenced by the stabilization of blood pressure, resolution of thrombosis, and improvement in laboratory findings. The role of the pediatrician in managing SLE and lupus nephritis during childhood and adolescence is essential in determining the type of distant prognosis the individual can expect as an adult. Regular check-ups, monitoring of symptoms and appropriate treatment are essential in preventing complications and improving the long-term outlook of the patient.

CONCLUSIONS

COVID-19 infection may trigger an unclear autoimmunity mechanism in a patient presenting the first symptoms of systemic lupus erythematosus. Intensive combination of immunosuppressive and anticoagulation therapies may lead to clinical remission and prevent adverse thrombotic events.

DISCLOSURES

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4. Conflicts of interest: None.

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