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PERIPHERAL ARTERIAL THROMBOSIS IN SYSTEMIC LUPUS ERYTHEMATOSIS AND NEPHROTIC SYNDROME: POSSIBLE ASSOCIATION WITH PROTEIN S DEFICIENCY*

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SUMMARY: Beşbaş N, Doğru D, Bakkaloğlu A, Özen S, Balkancı F, Saatçi Ü. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Peripheral arterial thrombosis in systemic lupus erythematosus and nephrotic syndrome: possible association with protein S deficiency. Turk J Pediatr 1997; 39: 143-147.

Arterial thrombosis in systemic lupus erythematosus (SLE) and nephrotic syndrome have been infrequently reported. A 16-year-old boy with SLE and longstanding nephrotic syndrome presented with peripheral arterial thrombosis when his lupus was at an inactive stage. He did not have antiphospholipid antibodies but had low serum antithrombin III and protein S levels. We suggest that the thrombotic event is not related to antiphospholipid antibodies but to nephrotic syndrome and possibly to acquired protein S deficiency. *Key words: arterial thrombosis, systemic lupus erythematosus, nephrotic syndrome, protein S deficiency.*

Thrombotic episodes have been reported as one of the manifestations of systemic lupus erythematosis (SLE), although arterial thromboses are less common[1]. Although vasculitis may play a role, there is increasing evidence that antibodies against phospholipids, namely anticardiolipin antibodies or lupus anticoagulant, may initiate clotting. On the other hand, thrombotic complications are also observed in nephrotic syndrome and are believed to be secondary to alterations in the coagulation and thrombolytic pathways[2]. Arterial thrombosis is much less common than venous thrombosis in this situation as well[3].

We report a patient with SLE and longstanding nephrotic syndrome presenting with peripheral arterial thrombosis who did not have antiphospholipid antibodies but had low serum levels of antithrombin-III (AT-III) and protein S.

Case Report

This 16-year-old boy was diagnosed with SLE four years previously with the following features: malar rash, erythematous macules on the extremities and trunk, fever, hepatosplenomegaly, proteinuria, cellular casts in the urine, anemia

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(Hb: 6.6 g/dl), low levels of C3 (37 mg/dl N: 60-120) and C4 (7 mg/dl, N: 20-40), positive antinuclear antibody and high anti-DNA titer (150 U/ml, N: 0-25). He was treated with methylprednisolone, cyclophosphamide and furosemide. While he was on maintenance therapy with low-dose prednisone, captopril and azathioprine, he was admitted to the hospital with a one-week history of dyspnea, edema of the face, abdomen and legs, and pain in the left hand.

Physical examination on admission revealed a dyspneic boy with a pulse of 128/min and respiratory rate of 32/min. His blood pressure was 180/140 mmHg. He had edema of the face, prominent on the eyelids, and of the scrotal region. His left arm and hand were cold and cyanotic, and the radial pulse of the same extremity was not palpable. He was unable to extend his left arm fully because of severe pain.

Laboratory examination revealed a white cell count of 9,600/mm^3 and platelet count 275,000/mm^3. His hemoglobin was 11.3 g/dl and hematocrit was 35 percent. Heavy proteinuria, leukocytes, red blood cells and granular casts were noted in the urine examination. Protein loss in the urine was calculated as 5 g/m^2/day. His total serum protein and albumin were 3.6 and 1.5 g/dl, respectively. The chest x-ray revealed pulmonary edema. The serum C3 level was 51 mg/dl (N: 60-120) and the C4 level was 19 mg/dl (N: 20-40). The antinuclear antibody test was negative. Anti-DNA was 6.7 IU/ml (N: 0-7). Prothrombin time (PT) (13 sec), partial thromboplastin time (PTT) (35 sec) and the test for fibrin degradation products were within normal limits. Anticardiolipin antibodies were measured by a sandwich ELISA kit (Biolab Malakit Cardiolipin isotyping kit). Results of the IgM and IgG fractions of anticardiolipin were expressed as MPL and GPL units, respectively. In our patient IgM and IgG fractions were less than 1 MPL U/ml (N: < 5) and less than 1 GPL U/ml (N: < 9). The patient had a normal protein C level of 105 mg/dl (N: 60-120) but a low protein S level of 27 (N: 73-210) as well as a low AT-III level of 13 mg/dl (N: 18-28).

Doppler ultrasonography revealed the absence of flow in the left brachial, radial and ulnar arteries. An aortogram and selective arteriogram via the right femoral route demonstrated an obstruction at the juncture of the left axillary left subclavian arteries (Fig. 1). An echocardiogram revealed normal heart valves without vegetations or intracardiac thrombus.

As the patient's renal function gradually deteriorated, hemodialysis was applied every other day via a subclavian catheter for two weeks. He was treated with rheomacrodex, vasodilators, furosemide, cyclophosphamide, prednisone and antiaggregants, and his complaints gradually subsided. After the 15^{th} day of treatment, the peripheral pulses of the left arm became palpable and the clinical findings in the same arm improved.

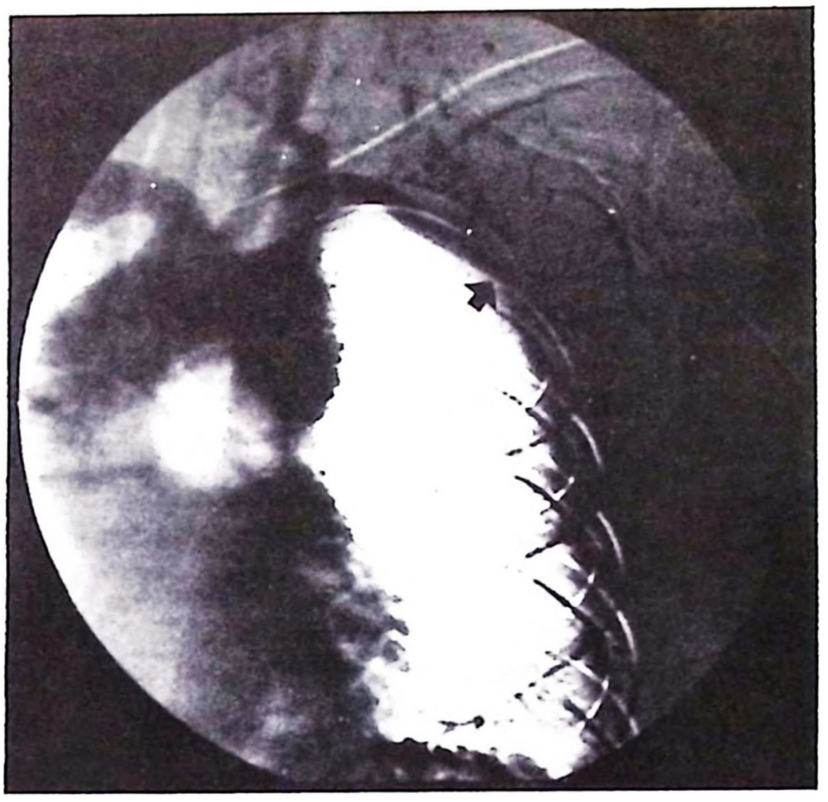

Fig. 1: Complete occlusion of the proximal portion of the left axillary artery and constriction at he origin of the brachial artery.

Discussion

The reported patient was diagnosed with SLE according to the American Rheumatism Association (ARA) criteria. Four years after the initial diagnosis he presented with arterial thrombosis when his lupus was at an inactive stage; however, he had longstanding nephrotic syndrome.

We evaluated 56 children with SLE who were seen at our center between 1978 and 1990. All eligible patients met at least four of the ARA's revised criteria for SLE. At the time of diagnosis, renal involvement was found in 69 percent of cases. None of the patients had a thrombotic event except a girl with SLE who had chorea as the initial manifestation and subsequently developed thrombotic events associated with the presence of antiphospholipid antibodies[4].

Thromboses may complicate the course of lupus. Asherson et al.[5] reported that in SLE patients with anti-phospholipid antibody (aPL), disease activity was an important predictor for the development of thrombotic events. Apart from aPL, there are other risk factors present in lupus, including depressed release of plasminogen activator and possibly antagonists of plasmin, decreased plasma concentration of free protein S and increased levels of von Willebrand factor as well as increased monocyte-derived procoagulant activity. Furthermore, when a child with lupus develops nephrotic syndrome, the thrombogenic potential of the

alterations in platelet function and plasma coagulation factors seen in nephrotics are added to the thrombogenic stimuli of lupus[6]. Our patient did not have active SLE at the time of the thrombotic event. Furthermore, he lacked aPL, which is one of the most important determinants of thrombotic events in SLE.

Thrombotic events have been previously reported in nephrotic patients and have been associated with acquired protein S deficiency[7]. Low AT-III levels together with other factors are a well-recognized feature of nephrotic syndrome and are believed to be due to excess urinary loss of AT-III[8]. In one study, AT-III levels were found to be normal and decreased in both primary nephrotic syndrome and primary amyloidosis, and it was concluded that AT-III levels were not only altered by urinary loss, but were also affected by the synthesis, degradation and distribution rate[9]. We suggest that our patient's arterial thrombotic event took place in the course of nephrotic syndrome with low protein S and AT-III levels. On the other hand, reduced free protein S concentrations have been suggested to be an important factor in the pathogenesis of venous thromboembolism associated with lupus anticoagulant as well[10]. Other factors for thrombosis in our patient may have been dehydration caused by diuretics plus corticosteroid therapy and hypoalbuminemia, which lead to a further decrease in intravascular volume.

We conclude that in SLE patients with longstanding nephrotic syndrome, especially those on diuretic and corticosteroid therapy, additional care must be taken to prevent a thrombotic event-even in those without antiphospholipid antibodies. In such cases, early diagnosis and medical treatment may avoid the need for surgical intervention.

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