



CASE REPORT

REVERSIBLE POSTERIOR LEUCOENCEPHALOPATHY IN AN 11 YEAR-OLD MALE CHILD WITH LUPUS NEPHRITIS

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ABSTRACT

Systemic lupus erythematosus is a chronic inflammatory disease characterized by highly diverse clinical manifestations. The major organ system involvements in childhood systemic lupus erythematosus are similar to those found in adults. Recognizing and reversing secondary causes of central nervous system abnormalities in patients with systemic lupus erythematosus are essential for preventing long-term neurologic disability or death.

In this manuscript, we present an 11 year-old male followed up in our clinic, who had the very rare involvement and complications of systemic lupus erythematosus in childhood. He developed a reversible posterior leucoencephalopathy after the first dose of cyclophosphamide, but cyclophosphamide therapy was not stopped as there was no clear evidence in the literature related to the role of this drug in reversible posterior leucoencephalopathy. The patient has now recovered.

Keywords: Childhood, Cyclophosphamide, Leucoencephalopathy, Systemic lupus erythematosus

LUPUS NEFRİTLİ 11 YAŞINDA ERKEK ÇOCUKTA GERİ DÖNÜŞÜMLÜ POSTERİOR LÖKOENSEFALOPATİ

ÖZET

Sistemik lupus eritematozus değişik klinik bulgularla kendini gösterebilen, kronik inflamatuvar bir hastalıktır. Çocuklardaki organ tutulumları erişkin ile benzerlik göstermektedir. Sistemik lupus eritematozuslu hastalarda santral sinir sistemi tutulumunun erken tanınması ve önlenmesi uzun dönem nörolojik komplikasyonlar ve ölüm açısından çok önemlidir. Bu yazıda; kliniğimizde takip ettiğimiz 11 yaşında, sistemik lupus eritematozusun çok nadir bir tutulum ve komplikasyonunu gösteren erkek hastayı sunmak istedik. Hastada siklofosfamidin ilk dozundan sonra reversibl posterior lökoensefalopati gelişti. Literatürde bu ilacın bu komplikasyonun gelişimindeki rolü açık olmadığından, ilacın kesilmesine gerek görülmedi ve buna rağmen hasta tamamen düzeldi.

Anahtar Kelimeler: Çocuk, Lökoensefalopati, Siklofosfamid, Sistemik lupus eritematozus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem inflammatory disease that can affect any and every organ system of the body. It is an autoimmune disorder involving multisystem microvascular inflammation and the generation of

autoantibodies. General clinical features include broad variations between the presence of rash, arthritis, constitutional symptoms, renal disease, cardiovascular, pulmonary, and neuropsychiatric involvement in any given patient. The major organ system involvements

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Marmara Medical Journal 2010;23(1);51-55



in childhood SLE are similar to those found in adults.

Neurologic or psychiatric abnormalities occur in up to two-thirds of patients with SLE¹. Neurologic symptoms may be classified as primary events (ie, resulting directly from immune mediated injury to the central nervous system (CNS)) or as secondary events (ie, related to complications of SLE or its treatment). Prospective studies have shown that at least 50% of neurologic abnormalities can be attributed to secondary factors, including drug toxicities, infection and metabolic complications of renal disease². Recognizing and reversing secondary causes of CNS abnormalities in patients with SLE are essential for preventing long term neurologic disability or death. Treatment of this disease which is accompanied by severe systemic involvement and complications is difficult and results are diverse.

In this manuscript, we present an 11 year-old male followed up in our clinic, who had the very rare involvement and complications of SLE in childhood. He developed reversible posterior leucoencephalopathy (RPLE) after the first dose of cyclophosphamide (CYC) given to treat persisting renal failure. CYC therapy was not stopped as there is no clear evidence in the literature related to the role of this drug in RPLE, and the patient has now recovered.

CASE REPORT

An 11 year-old male admitted to our clinic with fever, weakness, tiredness, blood in the urine, eruptions in the lower extremities, swelling, erythema, tenderness and local warmth in the knee, swelling in the testes and eyelids for the last 10 days. On physical examination, a depressive mood was recognized in addition to paleness and a tired look. His body temperature was 39°C and his blood pressure was 150/100 mmHg. He had pretibial (+++), scrotal and periorbital edema, ascites and arthritis in his right knee and widespread maculopapular and vesicular vasculitic eruptions in his lower extremities. His hemoglobin was 8,6 g/dL on admission, but his leukocyte, thrombocyte, and

reticulocyte counts, peripheral smear, PT, aPTT and INR were within normal limits and direct the Coombs test was negative. Among biochemical parameters BUN was 122 mg/dL, creatinine was 1,9 mg/dL, total protein and albumin were reduced and total lipid and cholesterol levels were elevated. A spot urine examination revealed macroscopic glomerular hematuria with a predominance of dysmorphic erythrocytes (>60%) and erythrocyte and granular casts at microscopic evaluation. Proteinuria was measured as 293 mg/m²/hr.

Renal ultrasonography (US) revealed increased kidney sizes and a renal parenchyma echo was found to be grade II. Renal colour-doppler US and renal arteriography were normal. With these findings, the patient was accepted as having a rapidly progressive glomerulonephritis, and a renal biopsy was performed; among the 19 glomeruli obtained, fibrinoid necrosis was present in five, and a diffuse proliferative glomerulonephritis with cellular crescents in 17. IgG and IgM (2 +), C₃ (3 +) granular depositions were found with immunofluorescent staining (type IV Lupus nephritis). ASO, CRP and RF were negative, IgA, G and M were normal, C₃, C₄ were very low. ANA was found to be positive while Anti-dsDNA was negative.

In view of these findings of the skin, joint, CNS and kidney involvement, the patient was diagnosed as SLE. Pulse methyl prednisolone treatment was started (1gr/day for 6 times on alternating days).

On the 2nd week of hospitalization, findings of renal failure, nephrotic and nephritic syndromes continued with persisting hypertension in spite of the use of diuretics, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers. As oligo-anuria developed, hemodialysis and pulse CYC therapy were started. The day after the 1st CYC dose the patient had a generalized tonic clonic seizure for 5 minutes which was controlled with diazepam. His neurological findings were normal during the post-ictal period. Fundoscopic examination was normal.



The electroencephalography (EEG) revealed slow baseline activity and cortical irritability in the left temporo-parieto-occipital region. A brain magnetic resonance imaging (MRI) was performed and findings of RPLE with increased signal intensities especially prominent in the left temporo-occipital region (Figure 1) were observed, as were signal intensities related to vasogenic edema by diffusion weighted imaging (DWI).

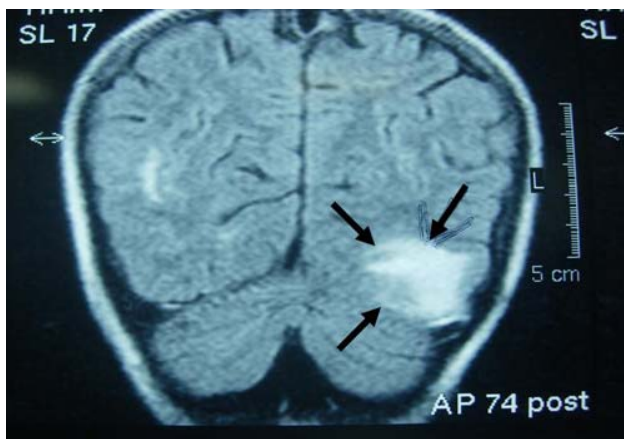


Figure 1: Brain magnetic resonance image after generalized tonic seizure in the patient with lupus nephropathy. Subcortical vasogenic edema in the right temporal and left temporo-occipital region (black arrow) observed as high signal intensities in coronal segments of T1 weighted images.

Hemodialysis was performed for a total of 7 sessions and prednisolone was given at a dose of 2mg/kg po.

On the 1st month during follow up, the uremia and renal failure were cured but findings of a nephrotic syndrome persisted. At this time a cardiac murmur was recognized and echocardiography revealed a 2x2 cm thrombus in the left ventricle. Anticardiolipin and antiphospholipid antibodies were negative, so the antiphospholipid syndrome was excluded and the thrombus was thought to be due to intravascular volume depletion as a complication of the nephrotic syndrome. After initial heparinization, the patient was treated with coumadin. Findings of RPLE in the control brain MRI were lessened (Figure 2).

Pulse CYC therapy was continued with decreasing doses of oral prednisolone and oral anticoagulants. Antihypertensives were stopped.

On the 4th month of follow up, the findings of the nephrotic syndrome were also cured and in addition renal functions were normal. Hypertension, CNS findings, cardiac thrombus, joint and skin findings were cured and C3, C4 levels, ANA and Anti-ds DNA returned to normal.



Figure 2: Brain magnetic resonance image 1 month after the initial magnetic resonance image. There is loss of the lesion in the right temporal region and a significant decrease in the high signal intensities related to the vasogenic edema in the temporo-occipital region (black arrow) in T1 weighted images.

DISCUSSION

The major organ system involvements in childhood SLE are similar to those found in adults; however the frequency and severity appear to be increased in children and adolescents^{3,4} Renal involvement appears to be more common and probably more severe in children and adolescents compared to adults, with estimates of prevalence ranging from 50 to 80% of all patients⁴. WHO lupus nephritis classes III and IV are reported to be the most common, similar to the case presented here. Our patient had the properties of both nephrotic and nephritic syndromes with severe hypertension, uremia, oligo-anuria, proteinuria, hematuria. These findings led us to perform a renal biopsy which revealed type IV lupus nephritis. During the



treatment period, the nephrotic syndrome persisted and as a complication, intravascular volume depletion developed, which in the end resulted in a cardiac thrombus, not one of the acute cardiac manifestations of SLE which are myocarditis, pericardial effusions, cardiac tamponade and sterile valvular (Libman Sacks) vegetations. On the other hand, our patient experienced a generalized tonic clonic convulsion, just one day after the CYC infusion which was started on account of the findings of persisting renal failure despite pulse methyl prednisolone therapy.

CNS involvement in SLE is very difficult to diagnose, assess and treat, but can lead to significant morbidity in children. Neuropsychiatric SLE has been reported in 29 to 44% of pediatric patients with SLE. Clinical manifestations in children have not been categorized, but include seizures, cranial nerve palsies, headaches, coma, psychosis, neuropathies, chorea, transient ischemic attacks, strokes, pseudotumor cerebri and encephalopathy⁵.

RPLE syndrome is a syndrome manifested by headache, nausea, vomiting, altered consciousness, seizures and visual disturbances including cortical blindness with predominant posterior involvement by neuroimaging. RPLE was first described by Hinchey et al in 1996⁶. It is a clinico-radiological entity, which appears on neuroimaging as reversible white matter edema predominantly involving the parietal and occipital lobes. The etiology of RPLE is believed to be due to a failure of cerebral autoregulation in a setting of severe hypertension, along with possible additive endothelial injury secondary to uremia, cytotoxic drugs and the formation of microthrombi. This results in a breakdown of the blood brain barrier with transudation of fluid and protein into the extravascular space resulting in cerebral edema. Another mechanism postulates cerebral vasospasm with resulting ischemia within the involved territories⁷.

Several studies have postulated a mechanism for the development of RPLE in SLE⁸. Garg⁹

on reviewing the literature suggests that immunosuppressive or cytotoxic agents could cause the syndrome via a toxic effect on vascular endothelium or endothelin-mediated vasospasm, or by a direct effect causing axonal swelling. CYC use has been reported in various cases of RPLE as in our case^{6,10,11}. The use of high-dose CYC commonly occurs in the setting of fluid overload, hypertension, and/or renal failure; therefore the exact contribution of CYC in inducing endothelial injury is not clear. In addition, there is no dose-risk relationship in the literature that enables one to determine a safe CYC dose to use. Some reports in the literature link the use of high dose steroids to RPLE^{10,12}, while others have used high doses to treat this syndrome with excellent clinical outcome^{12,13}. Due to the absence of exact evidence correlating CYC with RPLE in the literature, we continued pulse CYC therapy, which resulted in a cure.

Mukherjee et al⁷ reported that CT findings consist of a bilaterally symmetric low intensity in the posterior parietal/occipital lobes, whereas MRI demonstrates hyperintensity on T2-weighted images with the same distribution. The detected increase in brain water diffusion on MRI was related to vasogenic edema due to cerebrovascular autoregulatory dysfunction. Typically, on imaging, there is edema predominantly affecting the white matter of the parieto-occipital regions of the brain. The distribution is usually, though not always, symmetrical. Involvement of grey matter and other regions of the brain including brainstem, cerebellum, basal ganglia and frontal lobes have been reported. The involvement of posterior structures such as the cerebellum and brainstem is particularly common¹³.

Among several suggested mechanisms and risk factors for the development of RPLE in SLE, our patient had hypertension, endothelial injury secondary to uremia, cytotoxic drug treatment and formation of microthrombi. In our patient, we postulate that hypertension associated with renal failure, along with uremia, the possible role of vascular injury secondary to SLE, and lastly



the possibility of microthrombuses rising from the cardiac thrombus were likely contributing factors in the development of this syndrome.

Prasad et al.¹⁴, Casali-Rey et al.¹⁵, and Pavlakis et al.¹⁶ described pediatric cases of RPLE occurring with lupus nephritis and hypertension. Prasad et al.¹⁴ reported a female with lupus nephritis who developed leukoencephalitic changes, but these changes were not reversible. On the other hand, Casali-Rey et al.¹⁵ reported a hypertensive 19 year-old female with lupus nephropathy who developed RPLE and totally recovered. As far as we know, our case is the first male child reported in the literature who developed the findings of RPLE shortly after the diagnosis and onset of therapy for SLE. We think that termination of CYC in a case of RPLE is not necessary, until clear evidence correlating CYC with the pathogenesis of RPLE is available on medline.

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