Case Report

Complete resolution of juvenile neuropsychiatric lupus with low dose rituximab

Chanchal Gera[1], Gurpreet Singh Kochar[2], Sushma Sraw[3], Smriti Deswal[4]

From [1]Senior Consultant, Department of Medicine and Rheumatology, [2]Senior Consultant, Department of Pediatric Neurology, [3]Senior Consultant, [4]Senior Resident, Department of Radiodiagnosis, SPS Hospital, Ludhiana, Punjab, India

ABSTRACT

Nervous system involvement leads to high mortality in juvenile systemic lupus erythematosus. We present the case of a 12-year-old girl who was admitted with a history of recurrence of fever, cervical swellings, seizure, and delirium. Approximately 6 months back, she was started on antitubercular therapy (ATT) for fever and granulomatous lymphadenitis. She developed a recurrence of fever, new cervical swellings, seizures, and delirium while she was continuing ATT. Magnetic Resonance Imaging brain revealed multiple hyperintensities in bilateral basal ganglia, temporal, and hippocampal regions. The patient was diagnosed to have lupus based on clinical features, positive antinuclear antibody, positive double-stranded DNA antibody, and hypocomplementemia. To avoid cyclophosphamide-related gonadotoxicity in this young girl, Rituximab was given. She was treated with two doses of Rituximab and there was complete resolution of her neuropsychiatric SLE. Rituximab can be considered over cyclophosphamide in children to avoid gonadotoxicity.

Key words: Lupus, Juvenile, Neuropsychiatric, Rituximab

Juvenile-onset systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by autoantibodies directed against nuclear antigens. Juvenile systemic lupus erythematosus (jSLE) accounts for 15% of all SLE patients. The annual incidence of jSLE is estimated to be 0.36–0.9/100,000 children/year [1]. In 1999, the American College of Rheumatology published a set of neuropsychiatric SLE (NPSLE) case definitions, including 12 central nervous system (CNS) and 7 peripheral nervous system manifestations. The CNS manifestations were divided into four psychiatric syndromes and eight neurological syndromes. These were also divided into focal (events presenting as focal neurologic deficits) and diffuse (including cognitive disorder, mood disorder, psychosis, acute confusional state, and anxiety disorder) symptoms [2]. Studies have demonstrated the prevalence of neuropsychiatric symptoms of SLE to be around 90% [3]. However, when only major CNS manifestations such as psychosis, myelopathy, strokes, and seizures are considered, the prevalence falls to 4.3% [3]. Nervous system involvement is associated with high mortality in jSLE [4].

We report the case of a 12-year-old girl of NPSLE. This case is unique as the patient had shown complete clinical and radiological resolution of CNS involvement with a low dose of Rituximab.

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CASE REPORT

A 12-year-old girl presented with a 9-month history of fever and neck swelling and 10 days' history of altered mental status and seizures. The patient had been in her usual state of good health 9 months back when she developed fever, loss of appetite, weight loss, and bilateral neck swelling. She was evaluated elsewhere and Fine needle aspiration cytology (FNAC) of the cervical lymph node revealed granulomatous lesion but acid-fast bacilli (AFB) were not visualized. The patient was started on anti-tubercular treatment (ATT) there. Towards the completion of her 6 months of treatment, she developed jaundice and her ATT was modified. She again started having fever along with an increase in the size of cervical lymph nodes and multiple episodes of focal seizures. With these symptoms, she presented to our hospital. There was no history suggestive of photosensitivity, oral ulcers, joints pain, cola-colored urine, or Raynaud's phenomenon. There were no similar complaints in any of her first-degree relatives.

On presentation, she was awake but disoriented, not responding to commands appropriately. Spontaneous eye-opening was present but she was not making eye contact. Intermittent incomprehensible sounds were present. The girl was irritable and had an intermittent irrelevant talk. There was no focal neurological deficit. Her vital signs were normal but her weight was 26 kg (<3 SD). Examination revealed an axillary temperature of 100.2* F, poor nutritional status, icterus, and edema of lower limbs. She had near-complete alopecia. Multiple bilateral, non-tender,

Correspondence to: Chanchal Gera, Department of Medicine and Rheumatology, SPS Hospital, Ludhiana, Punjab, India. E-mail: cgera@rediffmail.com

1.5–2.5 cm size, soft to firm, non-matted cervical lymph nodes were palpable. The rest of the physical examination was normal.

Laboratory evaluation revealed thrombocytopenia (Platelet count - 82000/mm^3) with normal hemoglobin, leukocyte count (11.2 gm/dl and 5700/mm respectively), and high erythrocyte sedimentation rate (ESR) (91 mm/1st h). Kidney and thyroid functions were normal. Liver function tests revealed raised liver enzymes and low albumin levels (serum glutamic-oxaloacetic transaminase - 664 IU/L, serum glutamic-pyruvic transaminase - 158 IU/L, Serum protein - 5.2 gm/dl, albumin 2.2 gm/dl). Cerebrospinal fluid was acellular with raised proteins (115 mg%) and normal sugar (58 mg/dl with 80 mg/dl in the blood). Gram stain and AFB stain were negative. Cartridge-based nucleic acid amplification (CSF CBNAAT) for tuberculosis was also negative.

Magnetic resonance imaging (MRI) brain, axial T2/FLAIR images revealed asymmetrical abnormal areas of hyperintense signal in the right basal ganglia, cortical, and subcortical hyperintense signal intensities in the right temporal lobe, right hippocampus, and left deep basal ganglia (Figs. 1a and 2a). Leptomeningeal enhancement was also seen in the right temporal cortical and subcortical regions.

As she had alopecia, bicytopenia, and a high ESR, the possibility of autoimmune disorder was considered. Antinuclear antibody (ANA) was done by indirect immunofluorescence method and it was strongly positive in 1:1280 titers. Extractable ANA test revealed positive double-stranded DNA (dsDNA) antibody. Antiphospholipid antibodies were absent. Complement levels revealed hypocomplementemia C3 - 72 (84–168 mg/dL), C4 - 9.1 (13–44 mg/dL). The urine protein creatinine ratio was normal and urine microscopy did not reveal any microscopic hematuria, which essentially ruled out lupus nephritis. She was diagnosed to have SLE based on clinical features, positive dsDNA, hypocomplementemia, and exclusion of other possibilities.

She received IV Methylprednisolone pulse (30 mg/kg) for 5 days and two doses of Rituximab (375 mg/m^2) at 15 days' interval. One week after, the first dose of Rituximab, her consciousness improved markedly. Gradually, her general condition improved and she started accepting orally. By the 10th day, she started walking with minimal support. Within 3 months, she improved markedly in all aspects of health. Her alopecia reversed completely and now she has dense hair. Repeat MRI brain was done after 6 months of Rituximab which showed complete resolution of previous hyperintensities (Figs. 1b and 2b).

The patient has remained in good health since then and she is under regular follow-up for the last 15 months. At present, her steroid has been stopped and she is receiving azathioprine for maintenance of disease remission.

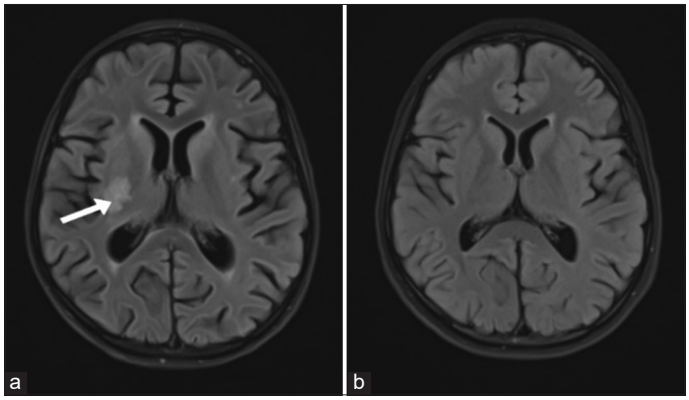

Figure 1: MRI brain, axial T2/FLAIR image showing asymmetrical abnormal areas of hyperintense signal in right basal ganglia (a-White arrow); Follow up MRI brain showing almost complete resolution of previously noted abnormal T2/FLAIR hyperintense signal (b)

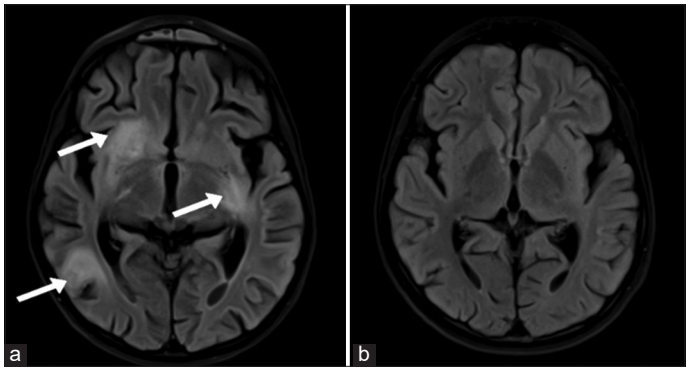

Figure 2: MRI brain, axial T2/FLAIR image showing abnormal cortical and subcortical hyperintense signal intensities in right temporal lobe, right hippocampus and in the left deep basal ganglia (a-White arrow); Follow-up MRI brain showing almost complete resolution of previously noted abnormal T2/FLAIR hyperintensities (b)

DISCUSSION

SLE has been described as the "disease with a thousand faces" due to the heterogeneity of clinical presentations. In index patient also, the diagnosis was delayed because of atypical presentation of SLE in the form of fever with lymphadenitis. The prevalence of lymphadenopathy in SLE is reported to be 26% [5].

Histologically, the lymph node lesions in SLE are characterized by varying degrees of coagulative necrosis with hematoxylin bodies or reactive follicular hyperplasia [6]. FNAC of the lymph node in our patient had revealed granuloma. Although granulomas are not commonly seen in SLE lymph nodes, few earlier reports had described noncaseating epithelioid cell granulomas consisting of the central zone of epithelioid cells surrounded by dense infiltrate of histiocytes [7]. In India, tuberculosis is a common cause of fever with granulomatous lymphadenopathy; hence, the patient was treated with anti-tubercular drugs.

In our case, lupus was diagnosed later when she developed new manifestations in the form of delirium and seizures. NPSLE was diagnosed after excluding infections, metabolic causes, and toxins exposure along with high titers of ANA, positive ds DNA, hypocomplementemia, and treatment response. According to a study by Sibbit *et al*., the common neurological manifestations in the pediatric SLE population are headache (72%), mood disorder (57%), cognitive dysfunction (55%), seizures (51%), acute confusional state (35%), peripheral nervous system dysfunction (15%), psychosis (12%), and stroke (12%) [8]. Differential

diagnosis of delirium in children with multifocal white and grey matter MRI lesions include viral Encephalitis, demyelinating disorders, primary CNS vasculitis, secondary CNS vasculitis, neurosarcoidosis, mitochondrial, DNA Polymerase Gamma-related disorders, and posterior reversible encephalopathy syndrome. As there is a paucity of clinical trials in NPSLE, information on treatment and outcomes is mainly derived from observational studies and extrapolated from experience with other organ system diseases in SLE and related disorders [9]. Immunosuppressive therapy in form of high-dose corticosteroids, azathioprine, cyclophosphamide, and mycophenolate mofetil is commonly used in the treatment of NPSLE. The first-line recommendation for significant CNS involvement in lupus is pulse steroids with cyclophosphamide and the second line is the addition of Rituximab, intravenous immunoglobulin, or plasmapheresis [10]. In a retrospective observational study of 18 NPSLE children who were treated with Rituximab, five had shown definite benefit, seven had shown probable benefit, five had shown possible benefits, and one did not show any improvement [11]. Narvaez and colleagues summarized all published data of adult patients with refractory NPSLE with Rituximab therapy, where a clinical response was observed in 85%, complete response in 50%, and partial response in 35% of patients [12]. Rituximab was preferred because of her young age and to avoid ovarian toxicity. In children, the most commonly used regimen is 375 mg/m^2 weekly for 4 weeks [11]. Given financial constraints, our patient had received only two doses of Rituximab (375 mg/m^2) at 15 days' interval instead of 4 weekly doses. Her consciousness, cognition improved remarkably and her alopecia reversed completely. At present, she has dense hair growth.

CONCLUSION

In children with NPSLE, cyclophosphamide-related gonadal toxicity is the limiting factor. As long-term safety is well proven for Rituximab, it can be considered in juvenile NPSLE. Additional controlled studies are needed to define the exact place of Rituximab and its doses in the therapeutic regimen for NPSLE.

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