

## A Case of Lupus Cerebritis in Dilemma: An Early Presentation of Overlap Syndrome or Mixed Connective Tissue Disease

Mehwish Farrukh<sup>1</sup>, Adil Ramzan<sup>2</sup>

### Abstract

We describe the unusual case of a teenage girl who was presented to a tertiary care center with unexplained acute encephalopathy preceded by long-standing severe headaches, irritability, cognitive impairment and ultimately altered level of consciousness. Her extensive workup was exceptional for abnormal Computerized Tomography (CT) scan suggestive of small and medium-vessel vasculitis, persistently elevated protein in the cerebrospinal fluid and steadily high titers of Anti Nuclear Antibody (ANA), anti-ribonuclear protein and anti-double stranded DNA antibody. Lupus cerebritis is a debilitating neurological complication confronted in rare patients of mixed connective tissue disease. We discuss a case of lupus cerebritis successfully diagnosed and treated. The coexistence of signs, symptoms and immunological features of 4 defined autoimmune diseases: systemic lupus erythematosus (SLE), systemic sclerosis (SS), polymyositis (PM) and rheumatoid arthritis (RA). The patient showed unpretentious response to intravenous high-dose methylprednisolone, azathioprine and hydroxychloroquine. Debate exists as to the best approach for treatment. Newer combination therapies based on anecdotal facts are suggested. We proposed that the patient's neurologic disease is secondary to immune-mediated central nervous system vasculitis, possibly as an initial manifestation of mixed connective tissue disease. Prompt diagnosis of lupus cerebritis is tremendously difficult because there is no single radiological confirmatory test and laboratory parameter. Assessment of clinical features, antibody detection and cerebrospinal fluid analysis lead to the diagnosis.

**Keywords:** Anti-double stranded DNA, antinuclear antibody, lupus cerebritis, polymyositis, anti-ribonuclear protein, systemic lupus erythematosus.

(ASH & KMDC 21(4):245;2016).

### Introduction

Neurologic demonstrations of rheumatic disease have been escalated for many years<sup>1</sup>. Classically, mixed connective tissue disease (MCTD) has

<sup>1-2</sup> Department of Medicine, Abbasi Shaheed Hospital, Karachi Medical & Dental College.

**Correspondence:** Dr. Mehwish Farrukh  
Department of Medicine, Abbasi Shaheed Hospital,  
Karachi Medical and Dental College  
Email: mehwishfarrukh92@gmail.com  
Date of Submission: 26<sup>th</sup> October 2016  
Date of Acceptance: 6<sup>th</sup> December 2016

not been associated with severe central nervous system (CNS) disease<sup>2</sup>. However, wide array of neurological manifestations are seen in 10%-20% of patients with MCTD included according to the frequency of occurrence, headache, seizure, aseptic meningitis, progressive multifocal encephalopathy, peripheral and trigeminal neuropathy and cerebellar ataxia<sup>1,3</sup>. MCTD is defined as a generalized clinical syndrome and characterized by the presence of high titers of antibodies to an U1 small nuclear RNP (anti-RNP), Rnase-sensitive ribonuclear protein

complex<sup>3</sup>. Presence of these antibodies is highly sensitive (>98%) for MCTD with a reported specificity of 60%<sup>3</sup>. High titers give a higher specificity which may go as high as 92%<sup>4</sup>. Matsui and co-workers reported a case of a 69-year-old woman with a diagnosis of MCTD that initially presented with neurological features<sup>1</sup>. We present the case of a Caucasian girl with encephalopathy and severe headache in the presence of high titers of anti-RNP and anti-dsDNA antibodies and imaging suggestive of small-to-medium-vessel vasculitis in the CNS. Lupus cerebritis occurring in patients with systemic lupus erythematosus (SLE) has been reported<sup>5</sup> but has not previously been described in mixed connective tissue disorder. We highlight the neurologic emergence as the early presentation of MCTD and emphasize the need to overlook MCTD as a probable diagnosis in the presence of rigorous CNS pathology. The case summary of this patient has been written after permission from her.

### Case Report

A 15 years old Caucasian girl with no prior psychiatric illness presented to emergency of Abbasi Shaheed Hospital, Karachi and admitted in Medicine Unit-1 in the month of May 2016, with altered mental status, irritability, high grade fever for 3 days and Glasgow Coma Score of 8/15, with a history of low-grade intermittent fever and joint pain and swelling for a duration of one year. She was also suffering from irregular menstrual cycles and menorrhagia. She was diagnosed by her primary physician as a case of severe rheumatoid-arthritis for which she has been prescribed Non-Steroid Anti-Inflammatory Drugs (NSAIDs). Nearly three months prior to admission; she began experiencing gradual worsening esophageal dysmotility and Raynaud's symptoms. Patient has not given any family history of connective tissue disease and belongs to low socio-economic class. On admission, the patient was noted to be febrile (102°F) mild tachycardia (heart rate 90/min), profound photophobia, multiple new erythematous plaques on bilateral cheeks in a malar distribution, old-neck poikiloderma, swollen hands and lips, sclerodactyly, mildly enlarged non-

tender liver, sub-ungal hyperkeratosis and synovial thickening in joints of hand and feet. On examination, planters were extensors bilaterally, power 3/5 in all four limbs, with decreased tone. Muscle bulk, cranial nerves and sensory examination was intact. Fundoscopy showed optic disc hyperaemia, blurred disc margins, with dilated veins, disc splinter haemorrhages and cotton wool spots. The provisional diagnosis of meningoencephalitis was made and treatment was initiated along with fluid and electrolyte correction. Haemoglobin was 6.2 gm per dl and the total white blood cell count (WBC) count was 6600 per cmm. Laboratory monitoring revealed mild elevations in ESR. The cerebrospinal fluid (CSF) study was not suggestive of infective pathology. Proteins was 94 mg/dl, total cell count 150 per cmm, normal glucose with 82% lymphocytes and the adenosine deaminase (ADA) test was negative. Arterial blood gas analysis showed mild metabolic acidosis. A CT scan of the brain revealed a moderate degree of cerebral edema and sub-centric opacities in right frontal and parietal region suggestive of vasculitis. Echocardiogram did not show any significant changes. Her level of alertness gradually deteriorated. Low-grade, intermittent fever persisted. The sepsis markers were not raised. A connective-tissue disorder was suspected. Laboratory tests were ordered accordingly. Laboratory investigations were remarkable for positive anti-ribonuclear protein (RNP) antibody and anti-double stranded DNA (anti-dsDNA) at high titers in the serum evident of mixed connective tissue disease. The patient was started on a course of high dose intravenous methylprednisolone (IVMP) (1 gram IV daily for 5 days). Her neurologic status showed modest improvement. She was able to follow one-step commands and respond to direct questions with simple sentences. Lupus cerebritis is a rare complication of MCTD; however, what makes this case even more intriguing is that it additionally had cerebral lesions consistent with neutrophilic vasculitis and cerebritis. Her mental status has progressively improved with normalization to baseline over a period of one week. Follow up visits to a tertiary care center every month demonstrated her normal mental state and on a tapered dose of steroids.



Fig 1. Showing sclerodactyly in fingers and calcinosis at PIP's and DIP's, deformity in small joints of hands and vasculitic lesions at pulp of fingers

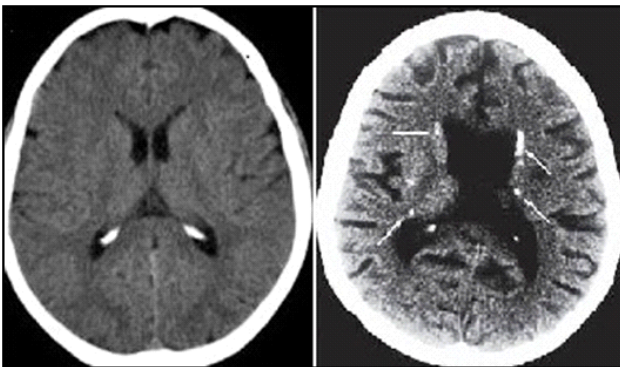


Fig 2. Multiple sub-centric opacities in frontal, parietal and paraventricular region indicating small and medium vessel vasculitis

## Discussion

Mixed connective tissue disease is a multisystem disorder with overlapping features of systemic lupus erythematosus, scleroderma, and polymyositis, and is differentiated from them by a high titer of antibodies to ribonucleoprotein<sup>1</sup>.

MCTD was first described by Sharp in 1972 and published in *The American Journal of Medicine*. Three sets of the MCTD diagnostic criteria exist in clinical practice those by Sharp, those by Alarcon-Segovia and Villareala, and those by Kasukawa<sup>2</sup>. The characteristic features of mixed connective tis-

sue disease are: 1) the presence of anti-U1snRNP antibody with high titers in sera, 2) an increased frequency of HLA-DR4 in the leukocytes, and 3) death due to pulmonary hypertension. Anti-RNP antibodies appear to be pathogenic, and their desertsion is associated with periods of remission in MCTD<sup>4</sup>. The onset of MCTD is typically at 15-25 years of age. Untimely presenting features in lupus cerebritis can be potentially confusing and can produce a significant diagnostic dilemma. The variety of neurological symptoms ranges from non-specific features like anxiety, headaches, seizures and depression whereas severe symptoms (visual disturbances, major seizures, dizziness, confusion or psychosis) are encountered in 18% of the cases. Early identification of lupus cerebritis is extremely challenging. No definitive radiological or laboratory test to reach the possible diagnosis has found<sup>5</sup>. Presence of antibodies in the serum and CSF, and evaluation of the clinical features are obligatory to conclude diagnosis. In association with other systemic manifestations of the disease or in isolation, CNS involvement of SLE may occur. A CSF study can indicate the possibility of CNS involvement in SLE by the presence of pleocytosis with a cell count 150 cells per mm<sup>3</sup>, with predominant lymphocytes. CSF also shows high protein levels in patients with lupus-Cerebritis<sup>6,7</sup>. Some researchers suggested that the presence of nitrates or nitrites in CSF could be used to assess the progress of cerebritis<sup>8</sup>. The neuron-reactive autoantibodies are seen in the CSF of 80% of the lupus cerebritis cases. CT scans in lupus cerebritis may show erratic features like normal brain or cerebral atrophy, calcification, infarcts, intracranial haemorrhage, or subdural fluid collections. Electro encephalogram (EEG) abnormalities are seen in 50 to 90% of the cases<sup>6</sup>.

The most frequent CNS manifestation is a trigeminal (fifth cranial) nerve neuropathy. Furthermore, neurological involvement of the MCTD usually includes, as per frequency of occurrence: headaches, sensorineural hearing, retinal vasculitis, cerebral hemorrhage, cauda equina syndrome,

transverse myelitis, progressive multifocal encephalopathy and demyelinating neuropathy.

SLE is suggested by the existence of antids DNA in her serum. In addition, our patient exhibit MCTD by the characteristic presence of both anti-RNP antibodies and high ANA titers (1:9,230). Titers in MCTD are considerably higher (usually >1:2,560) than those detected in SLE and are commonly used to differentiate the two clinical entities<sup>9</sup>. Additionally, by definition, patients with MCTD have features of several connective tissue disorders; in fact, most patients with MCTD will accomplish diagnostic guidelines for SLE and rheumatoid arthritis<sup>10</sup>. By manifesting signs of systemic sclerosis, SLE, and PM/DM, our patient clearly stays within the definition of MCTD as an "overlap" syndrome, independent of SLE.

We have described here a case of lupus cerebritis, with mixed connective tissue disease. The first patient had CNS involvement that represented meningoencephalitis. However, signs of meningeal irritation and pathological reflexes were found. The diagnosis of mixed connective tissue disease in this case relies on the presence of core clinical features of SLE, esophageal dysmotility, sclerodactyly, Raynaud's phenomenon, arthritis, high levels of anti-RNP antibodies. As a general condition patient improved and responded the treatment well. MCTD be considered as a diagnosis in patients presenting with neurologic impairment.

## Conclusion

We report a case of acute encephalopathy in 15 years old girl, in which after immense evaluations, high titers of anti-RNP antibodies were discovered and diagnosed as mixed connective tissue disease. Although she had a most concerning and dramatic presentation, she, so far, had responded very well to therapy including pulse dose steroids, followed by oral steroids tapering gradually according to the clinical symptoms azathioprine, and hydroxychloroquine.

## Conflict of Interest

Authors have no conflict of interests and no grant/ funding from any organization for this study.

## References

1. Goswami D, Chatterjee S, Ahmad BI, Das S. Two case reports indicating the dilemma in diagnosing lupus cerebritis. *J Family Med Prim Care* 2013;2:111-4.
2. Jacob A, Hack B, Chiang E, Garcia JG, Quigg RJ, Alexander JJ. C5a alters blood-brain barrier integrity in experimental lupus. *FASEB J* 2010;24:1682-8.
3. Lim JK, Kraus ML, Giles SS. Lupus cerebritis and steroid psychosis in mixed connective tissue disorder. *Yale J Biol Med* 2004;77:63-9.
4. Awad AM, Stevenson M. Isolated central nervous system vasculitis associated with antiribonuclear protein antibody. *Case Rep Neurol Med* 2011;2011:495201.
5. Jasinska D, Boczon J. Melkersson-Rosenthal syndrome as an early manifestation of mixed connective tissue disease. *Eur J Med Res* 2015;20:100.
6. Radulescu D, Pripon S, Ciovesescu F, Constantea NA. A rare case of systemic autoimmune disease with intricate features of systemic sclerosis, lupus, polymyositis and rheumatoid arthritis. Overlap syndrome or mixed connective tissue disease? *Acta Reumatol Port* 2007;32:292-7.
7. Kuroki M, Okayama A, Kuwata G, Okamoto M, Tanaka G, Iqa M, et al. [A case of mixed connective tissue disease with lupus-like manifestations of the central nervous system, successfully treated with cyclophosphamide combined with prednisolone]. *Ryumachi* 2000;40:627-32.
8. Tani C, Carli L, Vagnani S, Talarico R, Baldini C, Mosca M, et al. The diagnosis and classification of mixed connective tissue disease. *J Autoimmun* 2014;48:46-9.
9. Modjinou D, Gurin L, Chhabra A, Mikolaenko I, Lydon E, Smiles S. A case of systemic lupus erythematosus associated with longitudinal extensive transverse myelitis, cerebral neutrophilic vasculitis, and cerebritis. *Bull Hosp Jt Dis* 2014;72:294-300.
10. Küker W. Cerebral vasculitis: imaging signs revisited. *Neuroradiology* 2007;49:471-9.