

PRELIMINARY NEUROPSYCHIATRIC MANIFESTATION IN MIXED CONNECTIVE TISSUE DISEASE

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ABSTRACT

We report a case of 51 years old woman who suffered from mixed connective tissue disorder (MCTD), complicated by neuropsychiatric manifestation at her initial course of illness. This convoluted her case management, unless the diagnosis was confirmed by skin biopsy. She improved significantly and rapidly on steroid pulse. Neuropsychiatric characteristics are not common presentation in MCTD. Therefore, we propose that it's pertinent to evaluate the possibility of connective tissue disorders (CTD), irrespective of no suggestive systematic signs supporting the predominant neuropsychiatric presentation.

Key words: Mixed connective tissue disorder, Carpal tunnel syndrome, Psychosis, Parkinson's disease, Depressive disorder

INTRODUCTION

Mixed connective tissue disease (MCTD) is an entity with mixed features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/ dermatomyositis (PM/DM) and rheumatoid arthritis (RA), together with presence of high titer of anti U1 small nuclear (sn) anti-ribonucleoprotein (anti-RNP) antibodies.^{1,2} Anti-RNP is considered hallmark of diagnosis. Neurological manifestation is seen in MCTD ranging from 10-20%.³ Nonetheless, it's challenging to rule out connective tissue disorders (CTD) in patient with such characteristics at initial stage of the disease. We are presenting a case with prominent neuropsychiatric manifestations with negative anti-RNP, diagnosed later as a case of MCTD; ameliorated by steroid therapy. This case highlights the potential possibility of CTD in cases with neuropsychiatric features at first presentation.

CASE REPORT

Our patient was a 51-year-old Pakistani female, who presented initially with moderate depressive symptoms for four months. She was started on a SSRI with no clinical recovery. Subsequently she developed bilateral carpal tunnel syndrome (CTS), which was initially treated conservatively with medications with limited improvement and ultimately surgery. She also started having problems of vomiting and deteriorating weight followed by difficulty in standing up from a sitting position, cogwheel rigidity, tremors, ataxia and a shuffling gait. Parkinson's disease was suspected and a Dopamine agonist was introduced, which resulted in disorientation, auditory hallucinations, delusional misidentification, confabulation, restlessness, insomnia, low appetite, further weight loss of 25kg, incontinence, arthritis, alopecia and rashes on her lower back and front chest. Her condition further worsened with phases of catatonia and cognitive deficits. She was admitted in a local hospital and diagnosed as a case of primary psychotic illness. Later, early onset of Dementia was suspected. She was given antipsychotics, benzodiazepines, anticholinesterase, anticholinergics and small doses of steroids for knee pain, with no clinical improvement.

When she initially presented to us in this state, extensive workup was done. She scored 10/30 on her Mini Mental Status Examination (MMSE) showing impaired remote and recent memory, attention, abstraction and visuospatial capacity. Her vitals were raised with a heart rate of more than 130 and pressures of 160/100. Her body mass index was 20. On examination she had oral ulcers and a flat diffused rash on her upper chest. Her eyes had exophthalmos with left sided ptosis and a nodule on the left side of her neck. On neurological examination her cranial nerves were intact. Her motor examination showed wasted muscle mass with a power of 2/3 in all limbs along with hypertonia, hyperreflexia, down going plantar reflex and restricted flexion of her knee and elbow.

Blood analysis showed deranged thyroid functioning (TPO 44.8, TSH: 16 and FT4: 0.7). Complete blood count showed Hemoglobin of 9.9, LFTs were deranged, SGOT: 148, SGPT: 303, GGT: 754,AP: 200. Ferritin level was slightly raised to 338. HBA1C was 6.8; triglyceride was 233 with rest of the lipid profile in normal ranges. Anti nuclear antibody was positive, and ESR was 94. Extractable nuclear antigen (ENA) came negative along with complement 3 and 4. Some of these labs were initially negative and later became positive, probably due to low dose steroids that the patient had been on. Magnetic resonance imaging and angiography (MRA/MRI) showed small vessel disease, bilateral calcification in basal ganglia and cortical atrophy. Electroencephalography and Cerebrospinal fluid findings were unremarkable. Herpes simplex virus, herpes zoster virus, toxoplasma were negative. ECG showed premature ventricular contractions. Nonetheless, Holter and ECHO were normal. Rheumatoid factor, urea, creatinine, electrolytes, Vitamin B12, Calcium, Magnesium, Creatinine phosphokinase, urine detail report, HIV, Parathyroid hormone, Cortisol, serum Ceruloplasmin, 24 hour urinary copper, Hepatitis profile and folic acid were insignificant. Computed tomography of chest and abdomen were normal.

Skin biopsy of her rash on chest revealed a tissue fragment lined by epidermis, showing atrophic changes. The underlying dermis showed collagenization, minimal focal perivascular inflammatory infiltrate and increased dermal mucin. These finding were suggestive of MCTD.

She was the given corticosteroid pulse therapy along with Hydrochloroquine 400mg per day for three consecutive days. She initially developed manic features but within a week her mental status improved tremendously; ultimately returned to baseline.

DISCUSSION

There are four extensively used sets of diagnostic criteria's for MCTD, namely, the Sharp,¹ the Alarcon-Segovia,⁴ the Kasukawa and the Kahn⁵ criteria. The common thread to all the secriteria's is the prominent role of anti-RNP in the diagnosis. Only Sharp's criterion does not implicate anti-RNP as an imperative parameter for the diagnosis. Our patient can be diagnosed with MCTD on the basis of Sharp criterion. Nevertheless, Kasukawa is known to have a diagnostic sensitivity value of 75% in comparison to Sharp's 42%.⁶ It is established that anti-U1 RNP antibodies in CSF is a useful indicator for central neuropsychiatric symptoms, with 64.3% sensitivity and 92.9% specificity.⁷

Limited data is available on cognitive function and psychiatric presentation in MCTD. Benett et al⁸ noted 10% cognitive impairment (deficit in intelligence, attention, reasoning, learning, recall, fluency, language, and perceptual motor capacity), and Schedel et al⁹ observed 9% 'organic brain syndrome' in MCTD. The recent findings by Sauer et al,¹⁰ give higher figures of cognitive deficits of 20%. The prevalence of neuropsychiatric symptoms ranges from 5%¹¹ to 29% in an active stage of the disease.¹² Neuropsychiatric problems seen in MCTD include headache, convulsion, psychosis, encephalopathy, transverse myelitis, ataxia, aseptic meningitis, monocular blindness, trigeminal sensory neuropathy, polyneuropathy and entrapment neuropathy.^{10,11}

Our patient presented with predominant cognitive impairment, psychosis, and motor difficulties, and MCTD was confirmed by tissue biopsy. However, sensitivity of tissue biopsy in MCTD is low. Her clinical picture was further confused due to multiple different treatment regimens before she reached us. While we were unable to exclude Hashimoto encephalopathy, the clinical picture mentioned earlier along with findings of blood analysis are strongly suggestive of MCTD, given that the patient responded markedly on high dose pulse steroids.

It is not common to have neuropsychiatric manifestation at initial phase with underlying MCTD. It may lead to mismanagement to other viable possibilities of primary neurological disorder as Wernicke's Korsakoff, Dementia, Primary CNS angiitis, Binswinger' disease; primary psychiatric mood disorder or psychotic disorder. Therefore, we propose that this case can be added to the evidence supporting neuropsychiatric manifestations early in the course of MCTD.

It will be interesting to note that our patient had Carpal tunnel Syndrome in the early course of her illness, which was treated as a solo entity though she could have been suffering from synovitis cause by an inflammatory disease. It is commonly seen as an initial presentation of SLE and systemic sclerosis, but not many cases are reported to have CTS as a preliminary finding of MCTD.

The association of autoimmune diseases and hypertriglyceridemia may be overlooked, in particular in our patient who happened to have Hypertension and Diabetes Mellitus on her initial presentation along with high triglycerides. The IgA bound to purified human lipoprotein lipase and hepatic glyceride lipase, can suppress the activity of these enzymes.¹³ The lipase activity is inversely proportional to the level of circulating triglycerides. This may have been the case with our patient.

CONCLUSION

In this paper, we presented a case of a 51-year-old female with principal neuro-psychiatric complaints, who under-went extensive evaluation and was diagnosed to have MCTD; confirmed by tissue biopsy.

This case draws attention to the significance of evaluating for inflammatory diseases in a patient presenting with cognitive deficits, motor symptoms and psychosis. There is a viable probability of MCTD as an underlying pathogenesis of such presentations, even without evident systemic signs and absence of anti-RNP.

REFERENCES

1. Sharp GC, Irvin WS, Tan EM, et al: Mixed connective tissue disease-an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972;52:148-59
2. Minkin W, Rabhan N: Mixed connective tissue disease. *Archives of Dermatology* 1976;112:1535-8
3. Miyata M, Nishimaki T: Neural disorders in mixed connective tissue disease (MCTD) and overlap syndrome. *Ryoikibetsu Shokogun Shirizu* 2000;29: 279-81
4. Alarcon-Segovia D, Villarreal M: Classification and diagnostic criteria for mixed connective tissue disease, in *Mixed Connective Tissue Diseases and Antinuclear Antibodies*, edited by Kasukawa R, Sharp GC. Elsevier, Amsterdam, The Netherlands 1987, pp 33-40
5. Kasukawa R, Tojo T, Miyawaki S: Preliminary diagnostic criteria for classification of mixed connective tissue disease in *Mixed connective tissue disease and anti-nuclear antibodies*, edited by Kasukawa R, Sharp GC. Amsterdam, Excerpta Medica, 1987, pp 41-8
6. Cappelli S, Bellando Randone S, Martinovi D, et al: To Be or Not To Be, ten years after: evidence for mixed connective tissue disease as a distinct entity. *Semin Arthritis Rheum* 2012; 41:589-598
7. Sato T, Fujii T, Yokoyama T, et al: Anti-U1 RNP antibodies in cerebrospinal fluid are associated with central neuropsychiatric manifestations in systemic lupus erythematosus and mixed connective tissue disease. *Arthritis Care Res* 2010; 12: 3730-3740
8. Bennett RM, O'Connell DJ: Mixed connective tissue disease: a clinicopathologic study of 20 cases. *Semin Arthritis Rheum* 1980; 10:25-51
9. Bennett RM, Bong DM, Spargo BH: Neuropsychiatric problems in mixed connective tissue disease. *Am J Med* 1978; 65: 955-62
10. Nowicka-Sauer K, Czuszyńska Z, Majkiewicz M, et al: Neuropsychological assessment in mixed connective tissue disease: comparison with systemic lupus erythematosus. *Lupus* 2012;21: 927-933
11. Habets WJ, De Rooij DJ, Salden MH, et al: Antibodies against distinct nuclear matrix protein are characteristic for mixed connective tissue disease, *Clin Exp Immunol* 1983; 54: 265-276
12. Burdt MA, Hoffman RW, Deutscher SL, et al: Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. *Semin Arthritis Rheum* 1999; 42: 899-909
13. Brunzell JD, Miller NE, Alaupovic P, et al: Familial chylomicronemia due to a circulating inhibitor of lipoprotein lipase activity. *J Lipid Res* 1983; 24: 12-19