INTRODUCTION
Mixed connective tissue disorder (MCTD), initially known as Sharp's syndrome, was a term coined by Sharp himself and co-workers in the 1970's. MCTD consists of a constellation of signs and symptoms from different connective tissue disorders but mostly systemic sclerosis, SLE, rheumatoid arthritis (RA) and polymyositis/dermatomyositis in association with antibody directed against ribonucleoproteins (RNA-P). The natural history of MCTD predicts that within 5 years, nearly one-quarter of patients will manifest characteristic features of one of its four related connective tissue disorders, most commonly systemic sclerosis (21%), and less commonly SLE and rheumatoid arthritis. Neuropsychiatric manifestations are observed in 55% of patients presenting with MCTD with aseptic meningitis being the most manifestation. We present a case of MCTD in a female with predominant depression and seizures as the main neuropsychiatric complication.

CASE REPORT
An unmarried 38 years old female being treated for rheumatoid arthritis for the past one year presented with arthralgia, dyspnoea, progressive proximal muscle weakness, seizures, weight loss, dysphagia, alopecia, and dryness of the eyes and mouth with tightening of the skin. Psychiatric evaluation revealed major depression. She had oral ulcers, tightening of the skin of the hands with restricted mouth opening, and proximal muscle weakness. Mixed connective tissue disorder (MCTD) with predominant polymyositis and neuropsychiatric manifestations was diagnosed as the patient had anti-RNP positive with significantly raised muscle enzymes. This case is unique because major depression in MCTD is rarely documented, severe polymyositis is a rarity and ANA was negative but characteristic anti-RNP antibody was positive.

ABSTRACT
A 38 years female presented with arthralgia, dyspnoea, progressive proximal muscle weakness, seizures, weight loss, dysphagia, alopecia, and dryness of the eyes and mouth with tightening of the skin. Psychiatric evaluation revealed major depression. She had oral ulcers, tightening of the skin of the hands with restricted mouth opening, and proximal muscle weakness. Mixed connective tissue disorder (MCTD) with predominant polymyositis and neuropsychiatric manifestations was diagnosed as the patient had anti-RNP positive with significantly raised muscle enzymes. This case is unique because major depression in MCTD is rarely documented, severe polymyositis is a rarity and ANA was negative but characteristic anti-RNP antibody was positive.

Key Words: Mixed connective tissue disorder. Depression. Epilepsy. Polymyositis. Tonic clonic seizure.
total leucocyte count of 1600/uL (reference range 4000-1100/uL) with absolute neutrophil count of 550, microcytic hypochromic anaemia with haemoglobin of 6.98 g/dL (reference range 11.6 - 16.5 g/dL), platelet count of 66,000/uL (reference range 150,000-400,000/uL) and ESR 90 mm. Bone marrow biopsy was done. Serum electrolytes, renal and liver functions were normal. She was given one packed red blood cell transfusion followed by iron replacement therapy and intravenous ceftazidime and gentamycin to combat Pseudomonas infection during the neutropenic state.

The other investigations showed RA factor (quantitative) was negative at value < 10.0 IU/ml (positive > 50 IU/ml); anti-CCP was normal, 0.7 U/ml; ANA was negative; anti-dsDNA was also negative at 7.28 IU/ml; C4 was normal 0.39 g/L; C3 was low at 0.63 g/L, CPK (4500 U/L), LDH (7870 U/L), aldolase (10.2 U/L), and C-reactive protein (CRP at 72.4 mg/dl) were raised. TSH was normal at a value of 0.45 IU/mL and hepatitis B and C serology was negative. Routine examination of urine showed proteinuria ++ and 24-hour urinary protein was 389.9 mg. During her hospital stay, she developed one episode of generalized tonic clonic seizures. During this episode her metabolic profile, CT-scan brain, EEG, MRI brain and cerebrospinal fluid (CSF) analysis were normal. Bone marrow biopsy showed anaemia of chronic disease. She became critically ill on the 10th day of admission not responding to vocal or painful stimuli with a high grade spiking fever. Her complete blood picture showed a normal leucocyte count and platelet count with microcytic hypochromic anaemia. Blood and urine cultures were also negative. Repeat CSF analysis was again normal. It was at this time that the extractable nuclear antibodies showed anti-RNP- 2.92 U, anti-SS-A-5.41 U, anti-SS-B 1.31 U, anti-Sm 3.79 U, and anti-Scl-70 was 0.39U (positive greater: > than 1.0 U). She was started on intravenous methylprednisolone (1 G/daily) for 3 days followed by azathioprine and oral steroids (1 mg/kg/day).

The final diagnosis was MCTD with predominant polymyositis and neuropsychiatric manifestations in the form of depression and seizures. After starting treatment there was a dramatic improvement in her condition. She was discharged on oral steroid, azathioprine, valproate and escitalopram. On follow-up, this patient was stable with marked improvement in her symptoms and able to walk without support.

**DISCUSSION**

Initially most patients with MCTD present with non-diagnostic features, which are considered to represent an undifferentiated connective tissue disease (UCTD), before displaying clinical characteristics most consistent with a known disorder. This may be the possibility in this patient as well and the reason she remained undiagnosed prior to presenting to us, thus, requiring a high index of suspicion for diagnosis.

Neuropsychiatric manifestations are observed in 55% of patients presenting with MCTD. Aseptic meningitis being the most common, although psychosis, convulsions, peripheral neuropathy, trigeminal neuropathy, and cerebellar ataxia have also been described. This patient, however, did not have aseptic meningitis as proved by normal CSF analyses on two separate occasions, once she had generalized tonic clonic seizures and the other when she became critically ill with high grade fever followed by a state of unconsciousness which responded to corticosteroids and azathioprine.

This case is unique in several ways. Major depression in MCTD is rarely documented whereas psychosis and seizures do tend to occur. In a study of 20 patients with MCTD conducted by Bennett et al., over a span of 5 years, showed that 11 had neurological and psychiatric symptoms. Psychosis was seen in 3 patients, one patient also had a progressive stupor while severely ill with polymyositis very similar to this patient. Depression however, was not documented but can occur due to steroid use. Both depression and psychosis can occur because of steroid use but the dose is generally high about 40 mg and these symptoms occur early on after starting treatment and gradually disappear as the dose is tapered. This patient was not on steroids at the time of presentation or 3 months prior to admission and when she was given steroids in the past it was in a low dose (10 mg) and that too on irregular basis because of her diagnosis of RA. Secondly, the symptoms of depression improved with steroids, thus negating that steroids could be the cause of her illness.

This patient also had severe polymyositis as she had dysphagia to solids and proximal muscle weakness which rendered her bedbound and required support for her daily activities. Her muscle enzymes were markedly elevated which improved with steroid and azathioprine therapy. The only setback in this case was that she refused muscle biopsy as her condition was improving with normalization of muscle enzymes after treatment and electromyography was awaited. Subclinical polymyositis has been documented to occur in the beginning of MCTD but severe polymyositis is a rarity. It has been reported in 2 cases previously, one in a child and the other in an elderly female of African descent. The diagnosis of MCTD rests on the clinical manifestations and the presence of certain auto-antibodies. This patient was anti-RNP, anti-SS-A, anti-SS-B and anti-Sm positive but ANA, anti-dsDNA, and anti-Scl70 negative. Titres of ANA in MCTD are significantly higher (usually > 1:1,000) than those observed in SLE and are commonly used to distinguish the two clinical entities. This patient on the other hand was ANA negative but had the characteristic anti-RNP antibody which is diagnostic of MCTD. Although previously it was

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thought that the presence of anti-Sm antigen was an exclusion criterion for MCTD, it is now clear that this antibody is not specific for SLE and that both anti-dsDNA and anti-Sm antibodies can be seen transiently in patients with MCTD and that may be the reason why our patient was also anti-dsDNA negative and may become positive later on in the disease process.

The final diagnosis was MCTD with polymyositis, major depression and seizures as the main neuropsychiatric manifestation. MCTD may be difficult to diagnose initially because of the vague symptoms a patient may present with and thus a patient may remain undiagnosed and untreated.

REFERENCES