Tuberculous Meningitis: A Coexisting Infection in a Case of Mixed Connective Tissue Disease

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ABSTRACT

Mixed connective tissue disease (MCTD) is a systemic autoimmune disease having overlapping clinical features of at least two connective tissue diseases (CTDs), including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), and rheumatoid arthritis (RA) along with the presence of anti-U1-ribonucleoprotein (RNP) antibody. There is a wide spectrum of clinical manifestations. Most patients present with Raynaud's phenomenon, hand oedema, synovitis, myositis, and acrosclerosis. Generally, the presence of anti-RNP is associated with a good prognosis; however, the death rate is approximately 4% due to pulmonary hypertension, myocarditis, nephritis, and/or widespread vasculitis. The authors report a case of a young girl with MCTD along with concurrent tuberculous meningitis, a very rare occurrence.

Key Words: *Mixed connective tissue disease, Systemic lupus erythematosus, Anti-U1-ribonucleoprotein antibody, Tuberculous meningitis*.

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INTRODUCTION

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune disease. Alarcon-Segovia criteria (ASC) for its diagnosis include positive anti-U1-Ribonucleoprotein (RNP) antibody titre (>1:1600), myositis, and synovitis and 1 out of 3 clinical signs (Raynaud's phenomenon, swollen hands, and acrosclerosis).[1] The disease was originally described by Sharp in 1972.[2] The exact cause of the disease is not fully known. The disease is believed to have an underlying genetic predisposition and certain environmental and immune factors. Dernie *et al*. reported the incidence of this disease in UK as 5.1 per 100,000 adults per year.3 A Norwegian study revealed a female-to-male ratio of 3.3 to 1, and a mean age of diagnosis of 37.9 years.[3,4] There is a wide range of clinical findings with overlapping features of different connective tissue diseases (CTDs) and organ involvement. The most significant organs involved are the heart and lungs, presenting with pulmonary hypertension (PH), interstitial lung disease and myocarditis, which are leading causes of morbidity and mortality.[4] Steroids, antimalarials, mycophenolate mofetil, cyclophosphamide, methotrexate, and rituximab are treatment modalities.

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In the case of PH, vasodilators such as prostaglandins, endothelin receptor antagonists, phosphodiesterase 5 inhibitors such as sildenafil, and immunosuppression with corticosteroids and cyclophosphamide may be appropriate therapeutic considerations.

The authors present a case of an 18-year girl with MCTD who developed tuberculous meningitis (TBM) that turned out to be fatal.

CASE REPORT

An 18-year unmarried, female patient presented with complaints of an asymptomatic erythematous rash over the malar areas of the cheeks and bridge of the nose for two months (Figure 1 and 2). She had a history of fever, cough, and flu for the last three days. There was a history of photosensitivity, Raynaud's phenomenon, generalised body aches, and fatigue for the last three months, and pain in all joints but more in small joints of hands for the last two months.

Fever was monitored during her stay as high grade (101°F-103°F), intermittent, not associated with chills, night sweats, anorexia, and lumps/bumps in the body. The cough was mildly productive with white-coloured sputum.

On detailed inquiry, it was found that there was a previous hospital admission in the dermatology ward due to Steven Johnson syndrome secondary to the use of third-generation cephalosporin one year back. There were infrequent joint pains at that time with negative antinuclear antibody (ANA) and anti-dsDNA antibodies. She was labelled as having undifferentiated connective tissue disorder (UCTD) at that time but then she was lost to follow-up. Moreover, there was no history of weight loss or family contact with tuberculosis (TB).

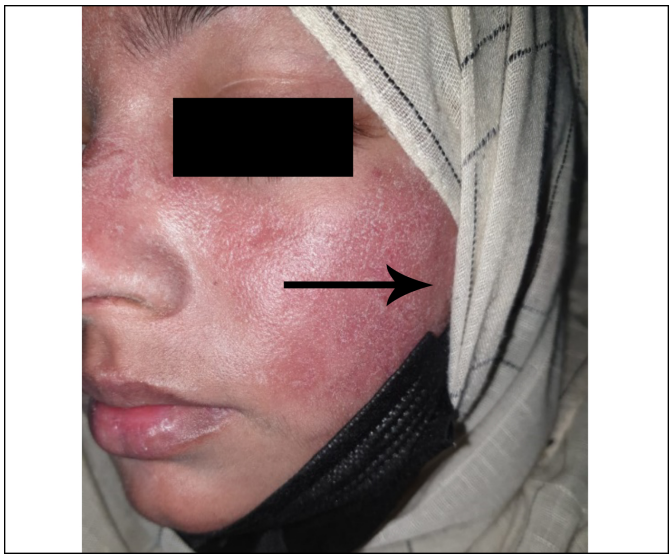

Figure 1: Malar rash (side view).

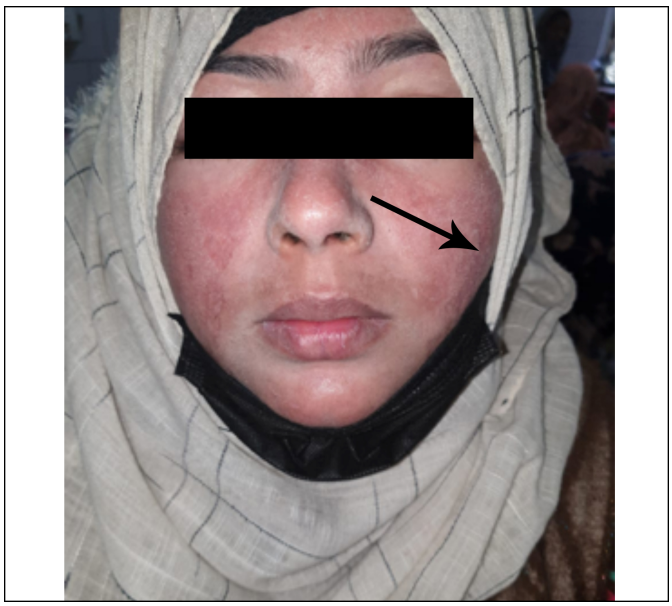

Figure 2: Malar rash on both sides.

Examination revealed positive Schuster sign, malar rash, oral erosions (on the hard palate), white coated tongue, hypertrophic scars on under the chin area, vasculitic lesions on palms of both hands, periungual erythema on most of the fingers around proximal nail folds and proximal muscle weakness. Scalp examination revealed non-cicatricial diffuse hair loss more in frontal and temporal regions.

Laboratory investigations revealed an Erythrocyte Sedimentation Rate (ESR) of 12 mm/1st hr, haemoglobin (Hb) of 10.4 g/dl (microcytic, hypochromic anaemia), and serum albumin of 2.7 g/dl. ANA was negative. No proteins were found in the urine and the rest of the labs were within normal limits. Chest x-ray (PA view) was normal. The patient was initially diagnosed as a case of Acute LE with upper respiratory tract infection and was started with an injection of dexamethasone 6 mg intravenous (iv) once a day (OD), injection of moxifloxacin 400 mg iv OD, capsule fluconazole 150 mg OD, and tablet of hydroxychloroquine (HCQ) 200 mg 12 hourly after eye examination for retinal changes, along with the daily application of 10% zinc oxide paste on the face in the morning, methylprednisolone acetate propionate cream in the evening and nystatin oral drops, 2 droppers on each side in oral cavity 6 hourly.

Among specific tests, her muscle enzymes were mildly raised: Lactate dehydrogenase (LDH) was 575 U/l (normal range: 140-280 U/l), creatine phosphokinase (CPK) was 193 U/l (normal range: 26-190 U/l), and alanine aminotransferase (ALT) was 74 U/l (normal range: 1- 40 U/l). Complete extractable nuclear antigen (ENA) profile revealed positive anti-U1-RNP, anti-Sm, anti-dsDNA, anti-ku, RP11 and RP 155 antibodies. C-reactive protein-high sensitivity (CRP-HS) was 3 mg/dl. So, she was labelled as a case of MCTD. Despite starting treatment, her fever did not respond and persisted at high grade. Blood and urine cultures were negative.

In addition to high-grade fever, she started developing mood changes, especially aggression and sleep disturbance in the next couple of days. Considering the possibility of lupus cerebritis, her neuropsychiatric evaluation was done. She had nausea, vomiting, and one episode of generalised tonic-clonic fits with upwards eye-rolling, which lasted for less than 1 minute with no associated tongue bite, and urinary / faecal incontinence. It was managed by injection of Diazepam. CT brain showed brain oedema and obstruction of ventricles. The neurologist on board suspected meningoencephalitis advised immediate lumber puncture and started with injection of Mannitol 150 mg iv 8 hourly, injection of benzyl penicillin 2.4 million units' iv 6 hourly, injection of Ceftriaxone 1 g iv 12 hourly, injection of acyclovir 1 g iv 8 hourly, injection of dexamethasone 4 mg/ml iv 8 hourly, and injection ondansetron 4 mg iv when required. The patient was shifted to the medical ward for lumbar puncture, and treatment was continued but the temperature kept on rising with deterioration of her Glasgow coma scale (GCS) to 11/15.

Her cerebrospinal fluid (CSF) report revealed lymphocytosis, raised protein, and normal sugar with a raised level of adenosine deaminase (ADA) in CSF of 23 U/l (normal: <5 U/l). She was diagnosed as a case of TBM and started with antituberculous treatment (ATT).

The patient's GCS deteriorated further till 4/15. Total leucocyte count (TLC) increased to 21×10^9/l, O_2 saturation dropped below 70% at room temperature, and she was shifted to ICU on a ventilator. Later, she developed ventricular tachycardia, leading to cardiac shock. She was cardioverted four times in emergency, and cardiac support along with amiodarone was started but she could not survive. The cause of death in this case, most probably, was myocarditis which is a complication of MCTD and of TBM as damaged heart muscle and scar tissue create abnormal electric pathways in ventricles leading to arrhythmias.[5]

DISCUSSION

MCTD is a rare autoimmune connective tissue disease. Systemic involvement is highly variable and includes arthritis,

myositis, cardiac involvement in 13–65% (pericarditis, myocarditis, coronary artery disease), pulmonary involvement (interstitial lung disease, pulmonary hypertension) and gastrointestinal dysmotility (50%). Renal disease may occur but is typically less severe than that observed in systemic sclerosis. Neurological or neuro-psychiatric features may be prominent but are usually less in frequency and severity than those seen in SLE.

Overall, the highest mortality rate has been found in young female patients having SLE duration <1 year and among the black African/American populations.

Neuropsychiatric features are being increasingly recognised in MCTD. The wide spectrum includes headache, peripheral neuropathy, aseptic meningitis, cerebral venous sinus thrombosis, and sensorineural hearing loss, with trigeminal neuralgia being the most common manifestation.[6] Though TBM is not mentioned in literature as part of CNS features of MCTD, it is a possibility that our patient living in a TB-endemic country acquired this infection. Another possibility is that the immunocompromised status of the patient due to her disease might be the reason either for catching the infection or to the reactivation latent TB, manifesting as extrapulmonary TB. Patients with CNS infections have more serious headaches, high-grade fever (>39.0°C), and vomiting compared with patients with lupus cerebritis or CNS involvement of MCTD.[6,7]

CSF is pale yellow in colour, contains an increased number of lymphocytes than neutrophils, is high in protein, and has less sugar than the corresponding blood sugar in TBM. Measurement of CSF ADA is the most frequently used immunodiagnostic method for TBM, which is a quick, easily available, and economical test. The ADA enzyme is released by T-lymphocytes with the cell-mediated immune response to tubercle bacilli. Recently, Palacios and Saleeb have reported sensitivity and specificity of 89% and 91%, respectively, for the diagnosis of TBM.[8]

A recent case series from China concluded that TBM patients have significantly longer SLE duration and decreased CD4+ cell counts and albumin levels than those without infections. Moreover, in patients with SLE declined CD4+ cell count was an independent risk factor for TBM.[9]

A cohort study from Indonesia pointed up that infection is a predominant cause of morbidity and mortality in patients treated with immunosuppressive agents. Among complications, infections such as TB must be considered, which are more frequently reported in patients of rheumatic diseases and SLE, especially for those living in TB-endemic areas.[10]

The authors have reported this case of MCTD complicated by TBM to highlight a few points. First, continuous high-grade fever in the case of CTD must alarm clinicians to think of both common and rare infectious causes. Second, a multidisciplinary approach is essential in such cases and must not be delayed for a better outcome. Lastly, during history taking, clinical examination, and relevant investigations, information should be gathered meticulously in challenging cases to reach a conclusive diagnosis and to ensure effective management.

PATIENT'S CONSENT:

Informed consent is obtained from the patient's attendants to publish the data concerning this case.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SI: Manuscript writing, review, editing, handling submission, and review process.

AS: Data collection and image acquisition.

AA: Conception of the main idea to report this case.

All authors approved the final version of the manuscript to be published.

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