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Cortical venous sinus thrombosis precipitated by rituximab in mixed connective tissue disease

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Abstract

Mixed Connective Tissue Disease (MCTD) is a rare autoimmune disease characterized by overlap of systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis and polymyositis; with high titer Antinuclear Antibodies (ANA) and anti-U1-RNP antibodies. We describe the first case of MCTD with class V Lupus Nephritis (LN) developing Cortical Venous Thrombosis (CVT) after Rituximab infusion. 28-year old female presented with features of lupus, limited systemic sclerosis and myopathy for 2½ years. Investigations revealed anaemia, class V LN, strongly positive ANA and anti- U1-RNP antibodies. Diagnosis of MCTD, class V LN with Grave's disease was made. She was initially treated with oral steroids, tacrolimus, hydroxychloroquine and cyclophosphamide. Later with Rituximab she developed large hemorrhage in right fronto-parietal region and extensive CVT. Central nervous system is rarely involved in MCTD and Antiphospholipid Antibodies (APL) are hardly seen. Only two cases of thrombosis during rituximab treatment are reported in literature and ours is the first case reporting CVT clearly due to rituximab.

Keywords

mixed connective tissue disease; lupus nephritis; rituximab; cortical venous thrombosis; anti phospholipid antibody syndrome; grave's disease

Introduction

Originally described by Sharp et al in 1972, Mixed Connective Tissue Disease (MCTD) is characterized by high titer anti-U1-RNP antibodies, and clinical and serological overlap of Systemic Lupus Erythematosus (SLE), rheumatoid arthritis, Systemic Sclerosis (SSc), and polymyositis [1]. It can have any class of Lupus Nephriris (LN), treatment of which is immune suppresants which includes biological anti- CD20 drug- Rituximab. This medicine has various adverse effects most common being infusion reactions and with increasing use some rare side effects are often recognized. Only four cases of thrombosis (non-cerebral/cortical) related to Rituximab uses are reported in literature. We present the first case of MCTD with class 5 LN developing Cortical Venous Sinus Thrombosis (CVT) after Rituximab infusion.

Case Report

A 28-year old, bedridden female from a rural background of India presented with progressive

weakness of muscles of all limbs, Raynaud's phenomenon and weight loss for the past 2½ years. It was associated with joint pains, dysphagia for liquids, hair-fall and fever for 6 months. On examination she was markedly cachectic with body weight of 22 kilograms. Physical examination showed digital pitted scars, mild thickening of skin with `salt and pepper' pigmentation over limbs and face, and proximal muscles power of 3/5 (Figures 1 and 2). There was no history of malar rash, oral ulcers, dry mouth or eyes, diarrhea and fetal loss. Last pregnancy was six years ago and she was not on any kind of hormone contraceptive.

Initial investigations are summarized in Table 1. Urine routine had 2+ protein without sediments, casts or cells and 24-hour urine protein excretion was 1.1 gm. 2D Echo had PAP of 42 and CT thorax showed mild NSIP pattern of Interstitial Ling Disease (ILD) at bases of lungs. Antinuclear Antibody (ANA) was positive in 1:1280 in speckled pattern with anti-dsDNA being negative. Anti- Scl 70 and anti- U1 Ribonuclear Protein Antibody (RNP) were strongly positive and other routine antibodies of extractable nuclear antigen were not detected. Kidney biopsy was suggestive of class V lupus nephritis. Because of muscle weakness and wasting, Electromyograph was done which reported myopathic pattern and muscle biopsy suggested endocrine myopathy. Skin biopsy was confirmatory of systemic sclerosis.

Final diagnosis of mixed connective tissue disease, class 5 lupus nephritis with Grave's disease was made. She was started on oral steroids, carbimazole, tacrolimus and hydroxychloroquine. For 3 months she had modest response where weakness in muscles improved, but proteinuria continued. She developed significant gastrointestinal symptoms and stopped taking tacrolimus. It was decided to start cyclophosphamide infusion, but with the first dose of 500 mg she experienced severe and persistent leukopenia (average TLC 1800 with PMNs 18 %), though no infection of any kind occurred. After 3 months of cyclophosphamide infusion when leukopenia improved, first infusion of 500 mg of Rituximab was given. However, 5 days after the infusion there were multiple seizures and right hemiplegia, caused by infarct in the left frontal region. Then she developed severe headache and loss of consciousness the next day when MRI of brain revealed large hemorrhage in right fronto-parietal region with midline shift due to superior sagittal sinus, right transverse and right sigmoid sinus thrombosis with normal intra-cranial arteries. Platelet counts, INR and routine blood investigations were normal. Thereafter emergency craniotomy and Antiphospholipid Antibodies (APL) testing were planned but she succumbed to her illness the next day.

Discussion

Of four published criteria for the diagnoses of MCTD, Alarcon-Segovia criteria is most favoured because of its simplicity, and high sensitivity and specificity (90% and 98% respectively) [2]. The criteria require high titer U1-RNP antibodies (defined as greater than 1:1600 with hemagglutination), and three of five additional signs: hand edema, synovitis, myositis, Raynaud's phenomenon, and acrosclerosis. All patients with MCTD will have a positive ANA in a speckled pattern with high titer U1-RNP autoantibodies especially to the 68 kD protein [3]. Patients with MCTD generally do not have positive anti-Sm, dsDNA, Scl-70, anti-centromere, or anti-Jo-1 antibodies. These patients are at high risk of ILD which has been identified in over 50 % patients [4]. The most common pulmonary findings are ground glass attenuation, non-septal linear opacities and peripheral and lower lobe predominance [5]. Isolated Pulmonary Artery Hypertension (PAH) is frequently detected and its prevalence is estimated at around 25 % [6]. MCTD is a

rare disease and point prevalence reported in Japan is 1.9 per 100,000 populations mirroring the prevalence in Norway which was 0.2/100,000 [7,8]. Overall survival in this disease is relatively favourable and 15-year survival is above 89.6% [9]. Less than 13% patients developed fatal complications in a Hungarian study of 33 years follow up where PAH alone was the commonest disease-associated cause of mortality contributing more than 40% deaths from all causes [10]. The absence of severe renal disease is a hallmark of MCTD and Membranous nephropathy being the most common renal manifestation whereas diffuse proliferative glomerulonephritis is much less common [1,11-13].

Central Nervous System (CNS) is rarely affected (only 10%) in MCTD wherein trigeminal neuralgia is the most common occurrence followed by vascular headache [1,14,15]. Other Neurological problems rarely seen in MCTD include seizures, psychosis, encephalopathy, transverse myelitis, ataxia, aseptic meningitis, monocular blindness, polyneuropathy and entrapment neuropathy. These features cluster in the dominant clinical syndrome seen in each patient of MCTD i.e. while Trigeminal and peripheral neuropathy tend to occur with predominant scleroderma features; optic neuropathy, transverse myelitis, encephalopathy and ataxia nests in patients with prominent SLE features [16]. There is only one case reported in MCTD developing massive putaminal hemorrhage without obvious predisposing factors [17]. In one case isolated CNS vasculitis was attributed to anti-RNP presenting as progressive encephalopathy whereas another author from Japan concluded that sub-acute cognitive decline, seizure and gait disturbance in their patient was due to MCTD [18,19]. Two girl child of MCTD with Cerebro-vascular disease were reported where one had left internal carotid artery occlusion while second girl died due to an intra-cerebral hemorrhage, autopsy of whom demonstrated small-vessel fibrinoid necrosis [20].

APL antibodies are rarely seen in MCTD and even if present, they rarely cause thrombosis or abortions; thrombocytopenia and PAH are more common manifestations [21,22]. A study by Komattireddy GR et al reported positive APL antibody in 15% of patients of MCTD and mirroring the results, about 13% of patients had these antibodies in an Indian study [22,23].

Lupus Nephritis (LN) is treated according to WHO class, age of patient and preferences expressed by patient. This patient did not tolerate cyclophosphamide, so rituximab was started as the next therapeutic option. Acute hypersensitivity reactions have been reported in patients receiving rituximab infusion manifesting as headache, fever, chills, sweats, skin rash, dyspnea, mild hypotension, and nausea. After extensive literature search we found two publications that reported thrombosis during rituximab treatment. First case reported seizures and acute Jugular venous thrombosis believed to be acute hypersensitivity reaction in diffuse large B-cell lymphoma during Rituximab infusion [24]. Acute venous thrombosis developed in one out of 38 patients after Rituximab therapy in lymphoma in second study, details of which are not published [25]. Rituximab is used in resistant or catastrophic APLS, however, in contrast, anecdotal reports show its association with thrombosis. Two cases are published from Japan, wherein thrombosis due to APLS in SLE was thought to be exacerbated by Rituximab re-infusion [26]. Transverse myelitis emerged in first patient due to formation of Human Anti-Chimeric Antibodies (HACA) after third course of Rituximab, while second patient developed catastrophic Anti-Phospholipid Antibody Syndrome (APLS) after Rituximab resulting in pulmonary embolism.

Our patient had fatal CVT due to Rituximab, may be due to APLS and to our knowledge, this is the

first case to be reported.

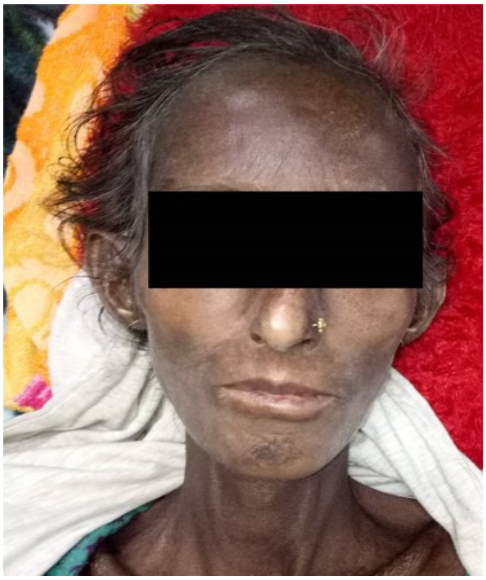

Figure 1: Muscle atrophy of face and "salt and pepper pigmentation" of skin.

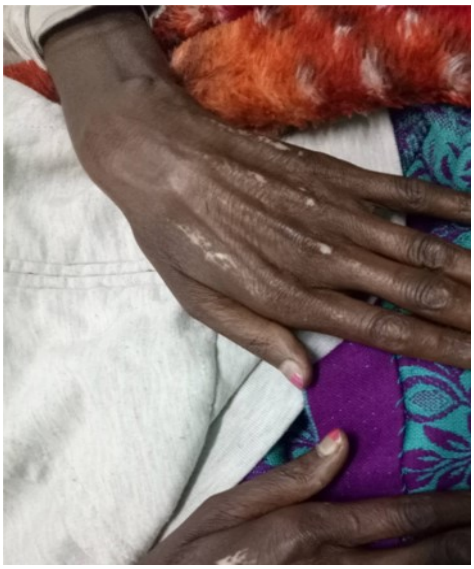

Figure 2: Severe atrophy of muscles of thigh.

Table 1

Hemoglobin	6.7 gm%
Total leukocyte count	4300/cu mm
Platelet count	142000/cu mm
ESR	14mm/1st hr
CRP	48 mg/L
SGOT	77 IU/L
SGPT	109 IU/L
Total protein	4.2 gm/dl
S albumin	1.8 gm/dl
S creatinine	0.6 mg/dl
Total CPK	64 IU/L
LDH	423 IU/L
TSH	0.01 mIU/L
T4	18 mcg/dl
Anti- TPO antibody	303 IU/ml

Conclusion

Rituximab is frequently used in lupus nephritis and other connective tissue diseases. Fatal thrombosis or precipitation of APS antibodies can occur during or after Rituximab therapy due to varying and complex mechanisms. A few cases of venous thrombosis after Rituximab are recorded and we report

a very rare but catastrophic outcome with Rituximab: As thrombosis of cerebral cortical veins which is being described for the first time. Irrespective if APS antibodies which may or may not had present, Rituximab precipitated the thrombosis. MCTD is a relatively innocuous disease and this patient died of drug-related complication rather than the disease.

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