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CASE REPORT

Lupus Cerebritis and Steroid Psychosis in Mixed Connective Tissue Disorder

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INTRODUCTION

Neuropsychiatric disease may occur commonly in mixed connective tissue disorder (MCTD) and has been observed in up to 55 percent of patients. Aseptic meningitis has been described as the most common presentation, although psychosis, convulsions, peripheral neuropathy, trigeminal neuropathy, and cerebellar ataxia have also been described [1, 2]. Corticosteroid therapy is highly effective in the management of CNS and systemic MCTD but may independently cause mood disturbances and psychosis; therefore, clinicians must carefully distinguish this entity from primary CNS disease [3-5]. Lupus cerebritis and steroid psychosis occurring in patients with systemic lupus erythematosus (SLE) has been reported [6] but has not previously been described in mixed connective tissue disorder. Herein we describe an individual with MCTD demonstrating both CNS MCTD and steroid-induced psychosis over two consecutive hospitalizations.

CASE REPORT

A 38-year-old African-American female with a five-year history of mixed connective tissue disorder (positive anti-RNP, ANA, anti-dsDNA, anti-Sm) and no prior psychiatric history presented to our hospital with altered mental status and MCTD flare. She had been clinically stable on prednisone 5 mg daily, plaquenil 200 mg twice daily, and ibuprofen as needed for several years. Nearly two months prior to admission, she began experiencing gradual worsening of her disease with more severe esophageal dysmotility and Raynaud's symptoms. Laboratory monitoring revealed mild elevations in ESR. The prednisone dose was increased to 5 mg each morning and 2.5 mg each evening two to three weeks prior to admission. In anticipation of starting methotrexate, liver function tests were obtained, and found to be mildly elevated. An abdominal ultrasound and CT of the abdomen/pelvis were normal.

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†Abbreviations: CTD, connective tissue disorder; MCTD, mixed connective tissue disorder; PM/DM, polymyositis/dermatomyositis; SLE, systemic lupus erythematosus.

She was admitted with high fevers, arthralgias, myalgias, severe esophageal dysmotility and Raynaud's symptoms, generalized weakness and fatigue, and a two to three week history of progressive alteration in mental status. This was described by family members as a markedly slow, labored speech, lack of insight into surrounding environment, nonsensical speech, poor concentration, emotional lability, and loss of inhibition. She was noted to carry conversation with imaginary figures, and chew on gum without first removing the wrapper. There was no history of substance abuse, tick bites, other toxic or outdoor exposures, or trauma.

Her exam was notable for fevers (102.3°F), mild tachycardia (HR 90), profound photophobia, multiple new erythematous plaques on bilateral cheeks in a malar distribution, old-neck poikiloderma, swollen hands and lips, mildly enlarged nontender liver, and synovial thickening in joints of hand and feet. Laboratory studies revealed anemia (Hg 8.8), leukocytosis (15,700), transaminitis (SGPT 66, SGOT 190), elevated ESR (113), and elevated CPK (1088). Disease activity was marked by positive ANA titer of 1:10,240 in homogenous pattern and diminished complement levels (C3<28, C4<10). Initial CSF studies demonstrated aseptic meningitis with monocytic pleocytosis (WBC 20, 100 percent monocytes, protein 40, glucose 51). All bacterial and viral cultures, India ink stain, RPR, and AFB were negative. Multiple imaging studies including a CT head, MRI brain, and EEG were also unremarkable. A diagnostic evaluation of elevated liver enzymes revealed negative HIDA scan and CT abdomen. In addition, initial ELISA screening for HIV was positive while the Western blot found to be indeterminate. Repeat testing of ELISA and Western blot, p24 antigen, and HIV PCR were subsequently confirmed to be negative.

She was diagnosed with MCTD disease flare with cerebritis, myositis, and hepatitis, and managed with an increase in corticosteroids to prednisone 40 mg daily. Over the course of a one-week hospitalization, the patient experienced significant improvement in her constitutional and rheumatologic symptoms as well as progressive normalization of her mental state to baseline. Due to a clinical suspicion for possible underlying HSV encephalitis, she was empirically treated with intravenous acyclovir, followed by oral famciclovir. HSV PCR testing was subsequently found to be negative. She was discharged in stable condition on prednisone 20 mg twice daily and plaquenil 200 mg twice daily.

She was re-admitted to our hospital seven days later with a three-day history of new mental status changes. In contrast to prior hospitalization, she was described by family members as hyperverbal with pressured speech, loosening of associations, flight of ideas, markedly elevated mood with euphoria and delusions of grandeur, significantly increased energy, sleeplessness, hyper-religiosity, and delusions of divine revelations. She described opening a multi-million dollar internet business to pay off debts of her friends and extended family, referred to a memoirs of her life on *The New York Times* bestseller list, and spoke under the pretense of divine authority. She reported no other complaints, and described marked improvement in all joint symptoms, esophageal dysmotility, Raynaud's symptoms, and skin disease, and denied the presence of fevers, chills, sweats, headaches, visual changes, or a stiff neck.

Upon examination, she was found to be hyperactive, pacing back and forth across the examination room, and hyperverbal with pressured speech. She repeatedly called to an imaginary dog outside the room, demonstrating active auditory and visual hallucinations. Her exam was notable for a normal temperature, mild

tachycardia (HR 110), notable improvement in her rash across the nasal bridge and bilateral cheeks, old poikiloderma of neck, minimal photophobia, absence of hand edema, and a normal abdominal exam. Laboratory data revealed continued anemia (Hg 7.8), normal chemistries and urinalysis, and minimally elevated ESR (45).

Following a formal psychiatric evaluation, a diagnosis of steroid-induced mania/psychosis was made. The prednisone dose was reduced from 20 mg twice daily to 20 mg once daily over several days, followed by 10 mg once daily at time of discharge. This was accompanied by the addition of a steroid-sparing immunosuppressive agent, azathioprine 50 mg twice daily, to prevent MCTD exacerbation, as well as a low-dose anti-psychotic to control her manic symptoms. Haloperidol 5 mg twice daily was initiated and quickly tapered to an as needed dosing schedule upon discharge. Her mental state progressively improved with near-normalization to baseline over a one-week period. Follow-up visits to her primary care physician two weeks and several months later demonstrated full normalization of her mental state and behavior off anti-psychotics and on a tapered dose of prednisone.

DISCUSSION

Our patient provides substantial evidence for two distinct manifestations of neuropsychiatric disease, one likely attributable to primary CNS involvement of MCTD and the other secondary to corticosteroid effect. Although neuropsychiatric disease appears to be common in connective tissue disorders, occurring in approximately 50 to 75 percent of patients with SLE [7, 8], and up to 55 percent of patients with MCTD [1], steroid-induced psychosis is uncommon. The condition is observed in less than 5 percent of patients with SLE [9] whereas its incidence in MCTD is unknown. The presence of CNS lupus and steroid psychosis in a patient with SLE has been previously reported by Hirohata and colleagues [6]. We believe this is the first reported case of both manifestations occurring in a patient with MCTD.

In the first episode, our patient presented with aseptic meningitis and other symptoms highlighting an exacerbation of her underlying mixed connective tissue disorder. This is corroborated by a congruence of historical factors (increased esophageal dysmotility, Raynaud's symptoms, articular complaints), exam findings (new rash, profound photophobia, hand edema, and articular disease), and laboratory markers (markedly increased ESR, transaminitis, and elevated CPK). In this setting, concomitant alterations in mental status were appropriately attributed to primary CNS involvement, particularly in light of a typical presentation for CNS MCTD. Aseptic meningitis (monocytic pleocytosis) is well-described as the most frequently observed sign of CNS involvement in MCTD, representing 20 percent of cases [1] More importantly, neuropsychiatric and somatic complaints improved in tandem upon initiation of aggressive corticosteroid therapy, further confirming the diagnosis. In the second episode, she presented with symptoms of frank mania, with profound euphoria, hyperverbality and pressured speech, sleeplessness, and delusions of grandeur. Historical factors (improved joint and skin symptoms, decreased esophageal dysmotility and Raynaud's), exam findings (healing rash, absence of hand edema, minimal photophobia), and laboratory markers (low ESR 45) clearly demonstrated improved, stable MCTD disease. Considering the context in which these mental status changes occurred (within one week of a significant increase in prednisone and in a setting of low disease activity), a corticosteroid-

induced effect appears to be the likely diagnosis. This is further supported by significant clinical improvement upon steroid taper.

Steroid psychosis, the product of steroid-induced vulnerability of hippocampal neurons to metabolic insults [10], most commonly presents with severe depression or frank mania. Symptoms of psychosis are less common, occurring in approximately 13 percent of patients. Most patients (57 percent) demonstrate these changes soon after starting or increasing corticosteroids, usually within the first two weeks, and typically at doses exceeding 40 mg daily (77 percent). Steroid taper is nearly always adequate in managing this syndrome (92 percent), although neuroleptics can be helpful. Symptom duration after initiating the taper is variable, although has a mean of 21 days [5]. In our patient, onset of manic symptoms began one to two weeks after dose increase, occurred at a total dose of 40mg daily, and responded to slow prednisone taper, albeit with support of a low-dose antipsychotic and steroid-sparing immunosuppresant. She returned to baseline mental state over a one to two-week period.

One may argue that external factors surrounding each episode may have contributed to our patient's neuropsychiatric disease. Many medications other than corticosteroids have been implicated as etiologies of acute mental status change in patients with rheumatologic disorders. Nonsteroidal anti-inflammatory agents, in particular, may induce an aseptic meningitis in patients with mixed connective tissue disorder, This has been reported in patients using therapeutic doses of ibuprofen [11, 12] and sulindac [13]. Accurate accounting of ibuprofen doses consumed by our patient prior to her first episode is not available and not specifically reported by the patient. No ibuprofen was used between initial discharge and second hospitalization. One would predict that in a state of increased disease activity on a subtherapeutic dose of corticosteroids, the number of breakthrough doses of ibuprofen would have increased. In the absence of this data, no conclusion can be made, although it is unlikely that in a setting of disease flare (and high incidence of neuropsychiatric disease in MCTD) that NSAIDs alone were responsible for her presentation with aseptic meningitis. More significantly, literature reveals that NSAIDs cannot account for her symptoms of psychosis in the first episode nor mania in the second.

HIV disease, too, can dramatically alter the differential diagnosis and management approach in a patient presenting with mental status changes. The initial positivity of HIV screening in our patient presented the medical team with several challenges, including proper assessment of the test's accuracy and clinical significance, and providing fair, objective counseling to the patient regarding these results. False positivity of ELISA testing and indeterminate Western blot results are well-described in patients with SLE [14] but is less certain in patients with MCTD. Clinicians must exercise caution in test interpretation in these patients, and must consider alternative diagnostic approaches for HIV infection [15]. HIV infection has been described as the new "great mimic" and certainly can present with neuropsychiatric disease [16] or manifestations of rheumatologic disease [17]. Notably, mixed connective tissue disorder, in particular, has profound clinical similarities with HIV infection. Anti-RNP antibodies cross-react with the HIV-1 surface due to multiple homologies between the gp 120/41 envelope complex and the 70 K protein of U1 snRNP, resulting in the ability of anti-RNP sera to effectively inhibit HIV-1 infectivity *in vitro* [18]. MCTD may, in fact, elucidate new strategies for development of immunologic resistance to

HIV infection (i.e., molecular mimicry). Fortunately, our patient was subsequently confirmed HIV-negative after repeat testing with standardized commercial assays, p24 antigen, and HIV PCR, and therefore HIV infection was an unlikely contributor to her neuropsychiatric disease.

One can additionally argue that primary CNS disease and steroid psychosis in our patient represented SLE rather than MCTD. This is clinically important in light of unique differences in natural history of disease and prognosis. Specifically, MCTD is characterized by significantly less renal disease [19, 20] and less morbidity and mortality from neuropsychiatric disease [21] but more severe arthritis and Raynaud's phenomenon, as well as an increased risk of death due to pulmonary hypertension [22-24]. Although this does not diminish the uniqueness of the case, the precarious nature of MCTD as a unique disease entity underlies the uncertainty in establishing a definitive diagnosis. MCTD is appropriately described as an undifferentiated connective tissue disorder (CTD) or "overlap" syndrome characterized by combinations of clinical features of SLE, systemic sclerosis, polymyositis/dermatomyositis (PM/DM), and rheumatoid arthritis [25]. Although several classification schemes have been described in literature, including three sets of criteria (Alarcon, Kasukawa, and Sharp), it is distinguished by the presence of high titer ANA and circulating autoantibodies to nuclear RNP antigen [26-28]. The natural history of MCTD predicts that within five years, nearly one-quarter of patients will manifest characteristic features of one of its four related connective tissue disorders [29], most commonly systemic sclerosis (21 percent), and less commonly SLE and rheumatoid arthritis [30]. One can hypothesize, therefore, that our patient differentiated from an "overlap" syndrome of MCTD into dominant SLE.

SLE disease is suggested by the presence of anti-dsDNA and anti-Sm antigen in her serum. Although previous authors have used the presence of anti-Sm antigen as an exclusion criterion for MCTD [28], 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 [31]. More importantly, our patient demonstrated MCTD disease by the characteristic presence of both anti-RNP antibodies and high ANA titers (1:10,240). Titers in MCTD are significantly higher (usually >1:2,560) than those observed in SLE [32] and are commonly used to distinguish the two clinical entities [33, 34]. Additionally, by definition, patients with MCTD have features of several connective tissue disorders; in fact, most patients with MCTD will fulfill diagnostic guidelines for SLE [35] and rheumatoid arthritis [36]. By manifesting signs of systemic sclerosis, SLE, and PM/DM, our patient clearly remains within the definition of MCTD as an "overlap" syndrome, distinct and independent of SLE.

CONCLUSION

Neuropsychiatric disease may occur commonly in patients with MCTD and can manifest as primary CNS disease or steroid-induced psychosis in the same patient. CNS MCTD presents most commonly as aseptic meningitis, in contrast to steroid-induced psychosis, which is characterized by severe mania or depression. Clinicians must carefully consider other secondary causes of mental status changes in these patients, including medications, metabolic derangements, and other comorbid conditions. The natural history of MCTD is dissimilar to its individual CTDs, and thus monitoring for differentiation is an important component of long-term management. Low-dose anti-psychotics and steroid-sparing immunosup-

pressive agents may represent helpful adjuncts to steroid taper in the management of steroid-induced psychosis.

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