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Major Depressive Disorder Following Dermatomyositis: A Case Linking Depression with Inflammation

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ABSTRACT *~ Major depressive disorder (MDD) is one of the most common psychiatric disorders. Recent studies have shown a strong association between MDD and peripheral inflammation, shown by a higher incidence of depression in patients with inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and systemic lupus erythematosus. Dermatomyositis (DM), an idiopathic inflammatory connective tissue disease that is associated with inflammation, predominantly affects the skin and skeletal muscle. The association between DM and MDD in the context of inflammation has seldom been reported. Here we report a 30- year- old Caucasian female with symptoms of depression dating back to 2 years. These symptoms started after cutaneous manifestations of DM. In the past two years, her DM symptoms have worsened that paralleled an increase of depressive symptoms. Also, during the course of the patient's DM, we tracked elevated inflammatory markers including creatine kinase and aldolase, whereas C-reactive protein, C3, and C4 were in a high normal range which correlated with worsening of depression. Hence, a temporal relationship between the onset of MDD and DM symptoms suggests that inflammation may be a common mechanism linking these two conditions.* Psychopharmacology Bulletin. *2018;48(3):22–28.*

Introduction

Major depressive disorder (MDD), a serious medical illness, is characterized by depressed mood and loss of interest or pleasure. MDD has a lifetime prevalence of about 17% in the United States and is also a leading cause of disability.[1–3] Studies have shown that many patients with MDD demonstrate increased circulating levels of acute phase proteins such as C-reactive proteins (CRP) and pro-inflammatory cytokines including interleukin-6 and tumor necrosis factor-α.[1,4–9] Also, increased numbers of activated microglia have been shown in the prefrontal cortex, anterior cingulate cortex and insula of MDD patients in a recent positron emission

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tomography imaging study suggesting that inflammation might also occur in the brain.[1,10] The severity of MDD symptoms correlates positively with an increase in pro-inflammatory cytokines.[1,11,12]

Pro-inflammatory states can also lead to depression. A classic example of this is the observation that the administration of interferons, which induce systemic inflammation, produce depression in about one-third of patients.[9] When depression occurs, it is largely indistinguishable from typical MDD,[13] and it can be treated or prevented with selective serotonin reuptake inhibitors'.[14,15] Other inflammatory conditions also show higher than expected rates of depression.[16] Various inflammatory disorders, including rheumatoid Arthritis (RA), inflammatory Bowel Disease (IBD), multiple sclerosis (MS) and their association with MDD are well documented.[1,17–20] Further, treatment of the underlying inflammatory state reduces depression, often prior to the improvement of the inflammatory disease.[21–24] Together, these findings indicate that inflammatory diseases are linked to depression.

Dermatomyositis (DM), an idiopathic inflammatory connective tissue disease, is a multisystem autoimmune disease with a wide range of clinical manifestations. Characteristics of DM include skin manifestations, muscle weakness with systemic symptoms including fever, arthralgia, dysphagia, dysphonia, and an increased risk of malignancy.[25–27] DM is characterized by several laboratory abnormalities including elevated levels of muscle enzymes such as creatine kinase (CK), lactate dehydrogenase, aldolase, aspartate aminotransferase, and alanine aminotransferase. Autoantibodies, including antinuclear antibodies, are also elevated. Elevated levels of serum and urine myoglobin are also seen in patients with DM.[25,27]

Even though patients with DM have a low quality of life, mental health problems are not well described in the literature related to DM.[17] Due to the dearth of the literature examining the relationship between MDD and DM, we are reporting a rare presentation of a patient with MDD followed by a diagnosis of DM and highlight the possible link between depression and inflammation.

Case History

A 30-year old Caucasian female presented to the outpatient psychiatry clinic in the latter part of 2016 with complaints of depression and anxiety. The patient also reported poor sleep, appetite, energy, motivation, feelings of hopelessness and worthlessness since March 2015 (after being diagnosed with DM). On initial presentation, she was diagnosed with MDD with anxious distress. Her depression started after she was diagnosed with dermatomyositis and became progressively more severe as her DM got worse.

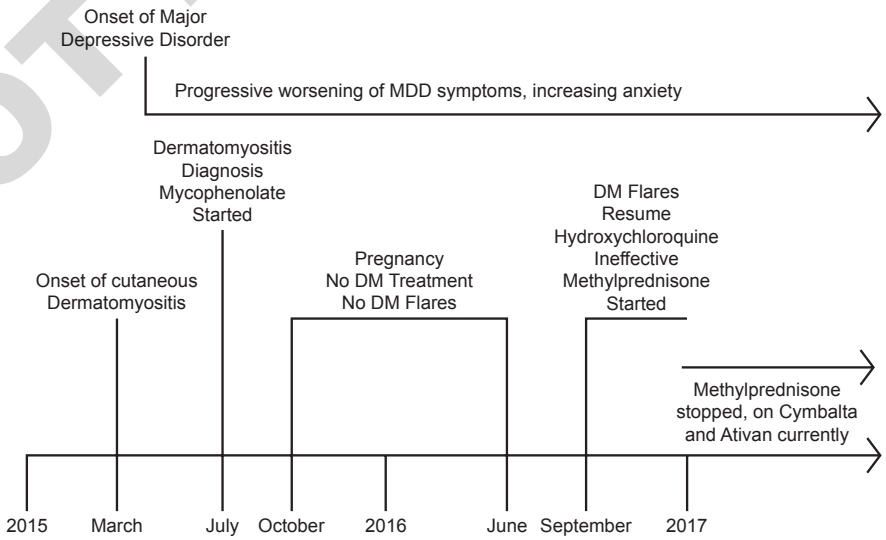
The patient did not have symptoms of MDD prior to March 2015, when she was initially diagnosed with contact dermatitis which was later changed to DM in July 2015. The patient was evaluated by a rheumatologist when she initially presented with a rash over face, neck, back, and hands accompanied by fatigue and body aches. Skin biopsy confirmed it to be DM. She was started on mycophenolate mofetil 500 mg orally daily for two weeks and then titrated to 500 mg twice per day.

She was diagnosed with MDD and started on escitalopram in November 2016. However, escitalopram did not help and was changed to citalopram and oxazepam (for anxiety) in December 2016. She did not benefit from this medication regimen and stopped it around June 2017. Cognitive behavioral therapy was also initiated in December 2016 in addition to medications. In January 2017, methylprednisone was stopped since she had worsening anxiety and depressive symptoms continued to progress. It was also noted that she had a flare up of DM characterized by increased joint and muscle pain, increase in CK and aldolase. As of October 2017, her depressive symptoms were getting progressively worse concurrent with her worsening DM symptoms. Currently she is on Cymbalta and Ativan for depression and anxiety (Figure 1).

There were no focal neurological findings or sensory deficits throughout. Due to her occasional headaches, a head MRI with and without contrast was done in August 2016 and showed no abnormalities.

FIGURE 1

Chronology of symptoms for Dermatomyositis and Depression



Changes in Inflammatory Markers During The Course of MDD (Table 1)

As summarized in Table 1, in line with the elevated inflammatory markers and worsening DM symptoms, depressive symptoms were concurrently worse during the same period. Thus in our case, CK and Aldolase were elevated higher than their normal range whereas CRP when trended was increased. C3, C4 were in high normal range.

Discussion and Conclusion

Mood symptoms have seldom been reported in patients with DM, an idiopathic inflammatory myopathy that is associated with a wide range of clinical manifestations, including involvement of skin, muscle, and other organs. Patients with DM have significantly lower quality of life when compared to other illnesses.[28,29] Here we present an association of MDD with DM, which has rarely been reported. The patient's worsening depressive symptoms seem to coincide with increasing inflammation associated with DM evidenced by a change in inflammatory markers, including elevated levels of CK and elevated level of CRP from her baseline. The levels of aldolase were also elevated.

A temporal relationship between the onset of MDD and DM symptoms in our case is evident. Further, during the course of the patient's DM, some inflammatory markers were tracked, and elevated levels of CRP (from baseline), CK and Aldolase corresponded to her worsening MDD symptoms. Both CK and Aldolase are markers of muscular inflammation. The elevation of theses markers strongly indicates the presence of inflammation. CRP is an acute-phase serum protein, which rises rapidly in response to inflammation. Both C3 and C4 levels were high, though in high normal range. Thus, we could hypothesize that inflammation could be a common mechanism underlying both DM and MDD and possibly linking them together.

TABLE 1

Changes in Inflammatory Markers During Course of MDD

MARKERS	AUGUST 2015	NOVEMBER 2016	JANUARY 2017	JUNE 2017	NORMAL RANGE
CK, unit	297 units/L		524 units/L	343 units/L	25–190 units/L
Aldolase, unit		13 units/L	16 units/L	11.6 units/L	1–7.5 units/L
CRP, unit	0.39 mg/L		1 mg/L		0.00–10.90 mg/L
C3, unit	100.9 mg/dL				87–200 mg/dL
C4, unit	29.4 mg/dL				19–60 mg/dL

Following the diagnosis of DM, immunosuppressants were started, but they were interrupted due to patient's pregnancy. Three months post-partum, she was restarted on an immunosuppressant that did not control her DM symptoms. It was noted that her depressive symptoms worsened at the same time due to non-adherence to antidepressants. Cognitive behavioral therapy was initiated to augment the antidepressant response, but it also was not effective.

It should be noted that although there is a clear link between inflammatory diseases and subsequent onset of depression and the current case suggests such a progression; this patient's depression may have been induced by other causes. These may include disfigurement due to the skin manifestations, pain, and psychological effects of having a serious medical condition, the anti-inflammatory treatments, pregnancy, and the post-partum state. It is impossible to identify the relationship between these types of factors and depression.

Since the association between inflammatory diseases and MDD is well documented, patients with autoimmune disorders should be screened for depression. Our case report also highlights the value of involving multidisciplinary specialties' including dermatologists, rheumatologists, psychiatrists and therapists to the care of inflammatory conditions like DM with concurrent MDD.

In summary, inflammation appears to be a common mechanism in both DM and MDD. In the present case, the onset and worsening of depression appeared to parallel the DM and systemic inflammation. This case highlights the need for screening patients with autoimmune diseases for MDD. Timely access to mental health and multidisciplinary approach towards treatment of concurrent MDD conditions may improve outcomes and quality of life for patients. ✤

Authors and Contributors

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Disclosure of Potential Conflicts of Interest

Drs. Reddy, Birur, Shelton, and Li have no conflict of interest to disclose in the preparation of this manuscript.

References

1. Money KM, Olah Z, Korade Z, Garbett KA, Shelton RC, Mirnics K. An altered peripheral IL6 response in major depressive disorder. *Neurobiology of disease*. 2016;89:46–54.
2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*. 2005;62(6):593–602.
3. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370(9590):851–858.
4. Dahl J, Ormstad H, Aass HC, et al. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. *Psychoneuroendocrinology*. 2014;45:77–86.
5. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446–457.
6. Erdem M, Celik C, Cayci T, et al. Serum haptoglobin levels in patients with melancholic and nonmelancholic major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2011;35(4):944–947.
7. Maes M, Scharpe S, Meltzer HY, et al. Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. *Psychiatry Research*. 1993;49(1):11–27.
8. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine*. 1997;9(11):853–858.
9. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology*. 2006;27(1):24–31.
10. Setiawan E, Wilson AA, Mizrahi R, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry*. 2015;72(3):268–275.
11. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine*. 2009;71(2):171–186.
12. Yirmiya R, Pollak Y, Morag M, et al. Illness, cytokines, and depression. *Annals of the New York Academy of Sciences*. 2000;917:478–487.
13. Capuron L, Fornwalt FB, Knight BT, Harvey PD, Ninan PT, Miller AH. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? *J Affect Disord*. 2009;119(1–3):181–185.
14. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med*. 2001;344(13):961–966.
15. Kraus MR, Schafer A, Schottker K, et al. Therapy of interferon-induced depression in chronic hepatitis C with citalopram: a randomised, double-blind, placebo-controlled study. *Gut*. 2008;57(4):531–536.
16. Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. *Neuro Endocrinology letters*. 2011;32(1):7–24.
17. Achtman J, Kling MA, Feng R, Okawa J, Werth VP. A cross-sectional study of untreated depression and anxiety in cutaneous lupus erythematosus and dermatomyositis. *Journal of the American Academy of Dermatology*. 2016;74(2):377–379.
18. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosomatic Medicine*. 2002;64(1):52–60.
19. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflammatory Bowel Diseases*. 2009;15(7):1105–1118.
20. Lo Fermo S, Barone R, Patti F, et al. Outcome of psychiatric symptoms presenting at onset of multiple sclerosis: a retrospective study. *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2010;16(6):742–748.
21. Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. *Ann Rheum Dis*. 2010;69(1):222–225.
22. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet*. 2006;367(9504):29–35.

23. Dauden E, Griffiths C, Ortonne JP, et al. Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *J Eur Acad Dermatol Venereol*. 2009;23:1374–1382.
24. Raison Cl RREWBJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *Archives of General Psychiatry*. 2012:1–11.
25. Bohan A, Peter JB, Bowman RL, Pearson CM. Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. *Medicine*. 1977;56(4):255–286.
26. Tymms KE, Webb J. Dermatopolymyositis and other connective tissue diseases: a review of 105 cases. *The Journal of Rheumatology*. 1985;12(6):1140–1148.
27. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. 2003;362(9388):971–982.
28. Ramanan AV, Sawhney S, Murray KJ. Central nervous system complications in two cases of juvenile onset dermatomyositis. *Rheumatology (Oxford, England)*. 2001;40(11):1293–1298.
29. Goreshi R, Chock M, Foering K, et al. Quality of life in dermatomyositis. *Journal of the American Academy of Dermatology*. 2011;65(6):1107–1116.