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Case Report

Efficacy of Milk Thistle in a Patient with Systemic Lupus Erythematosus Presenting with Autoimmune Hepatitis

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Abstract

A 68-year-old woman with Systemic Lupus Erythematosus (SLE) since 1990, and treated with hydroxychloroquine, was diagnosed with Autoimmune Hepatitis (AIH) in 1998. Her AIH was characterized by elevation of liver enzymes, hypergammaglobulinemia, and positive anti-smooth muscle antibodies. Initially, she was treated with prednisone achieving partial control. However, prednisone dose could not be decreased below 15-20 daily and eventually caused several drug toxicities. Treatments with azathioprine and mycophenolate mofetil were discontinued due to severe adverse events. Hydroxychloroquine was discontinued in 2016 due to retinal toxicity. In 2016, she started milk thistle (Silybum marianum) resulting in a favorable clinical response, with normalization of liver enzymes levels and retarding the progression of her hepatic disease. Moreover, it was effective to maintain her SLE well controlled and without exacerbations. This report, together with the known anti-inflammatory and immunomodulatory effects of milk thistle, suggests that it may be of benefit for patients with autoimmune disorders.

Keywords: Milk thistle; Silybum marianum; Systemic lupus erythematosus; Autoimmune hepatitis

Introduction

Autoimmune Hepatitis (AIH) is a chronic hepatic inflammatory disease. T cell dysfunction seems to be crucial in the pathogenesis of this condition, although B cell abnormalities have also been described [1]. Several autoantibodies have been found in these patients, including Antinuclear Antibody (ANA), anti-smooth muscle antibody (ASMA), Anti-Liver Kidney Microsomal-1 antibody (ALKM-1), and Anti-Liver Kidney Microsomal-3 antibody (ALKM-3), among others [2]. It is more common in women and its clinical presentation varies widely, from asymptomatic elevation of liver enzymes to acute liver failure and chronic liver disease [2]. AIH occurs as a primary disorder or in association or coexistence with other autoimmune rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and mixed connective tissue disease [3]. Up to 30 to 50 % of AIH patients develop cirrhosis. Furthermore, they are at greater risk for hepatocellular carcinoma [4]. Therefore, early recognition and treatment are crucial. Initial therapy includes corticosteroids as monotherapy or in combination with azathioprine [5].

For patients resistant to these drugs or those who develop serious adverse events, other immunosuppressive agents such mycophenolate mofetil or tacrolimus have been proposed, but clinical data are limited. Therefore, alternative therapeutic options are required. Herein, we present a woman with SLE who developed AIH. She failed or developed severe adverse events to immunosuppressive drugs. Instead, treatment with milk thistle or Silybum marianum, a plant with known antioxidant and immunomodulatory effects, was safe and effective to control both her AIH and SLE.

Case Report/ Case Presentation

This is a 68-year-old woman who developed SLE in 1990 manifested by discoid lupus (biopsy proven), leukopenia, lymphopenia, positive ANA (1:640; homogeneous pattern), elevated anti-dsDNA and anti-Ro antibodies, and C4 hypocomplementemia. She was treated with intralesional corticosteroid injections and hydroxychloroquine. The latter was discontinued in 2016 due to toxic retinopathy.

In 1998, she presented with elevation of liver enzymes levels: aspartate aminotransferase (AST) of 248 U/L (normal range: 0-40 U/L), alanine aminotransferase (ALT) of 265 U/L (normal range: 0-48 U/L), and alkaline phosphatase (AP) of 270 U/L (normal range: 30-117 U/L). She had no history of alcohol consumption and did not take medications known to cause liver injury. She had no anorexia, weight loss, fatigue, jaundice, nausea, abdominal pain, gastrointestinal bleeding, arthralgias, or urticaria. She had no coagulopathy, hypoalbuminemia, or elevated bilirubin levels. ASMA levels were elevated at a titer of 1:640. Serum protein electrophoresis showed elevated gamma fraction at 2.9 g/dl (normal range 0.7-1.7 g/dl). Anti-mitochondrial, ALKM-1, ALKM-3, and anti-neutrophil cytoplasmic an-

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tibodies were negative. Serum levels of ceruloplasmin, ferritin, transferrin, total iron, total iron binding capacity were normal. Serum panels for hepatitis B and C were negative. No hepatomegaly or splenomegaly was seen in the abdominal sonogram.

She was treated with prednisone (maximum dose of 40 mg daily). Liver enzymes levels significantly decreased, but mainly remained around 2 times the upper limit of normal. She was unable to decrease prednisone dose below 15-20 mg daily. She developed several adverse events to corticosteroids including Cushingoid features (buffalo hump, moon face, and hirsutism), dyslipidemia, and osteoporosis. She was briefly treated (<1 month) with azathioprine and later with mycophenolate mofetil, but these drugs were discontinued due to severe abdominal pain, nausea, and vomiting. Eventually, her liver disease progressed. Serum albumin levels decreased down to 3.2 g/dl. Vibration-controlled transient elastography done in November 2014 showed a mean liver stiffness score of 15.4 kPa consistent with fibrosis stage 3.

In 2016, she started to take milk thistle; one tea bag containing 3 g of organic milk thistle seeds (5% silymaryn) twice daily. Two years later, she switched to capsules (standardized milk thistle extract (seed) 100 mg (total flavonoids including silymarin 80 mg) and milk thistle powder 350 mg (aerial, seed)) twice daily. Milk thistle was well tolerated and did not cause adverse events. She had a favorable clinical response to milk thistle. After six months of therapy, ALT an AP levels decreased and remained within normal levels. AST levels decreased to almost normal levels. Figure 1 shows trends of AP, AST, and ALT levels before and after milk thistle treatment. Albumin levels increased to 4.2 g/dl. Real-time abdominal ultrasound showed no hepatomegaly or splenomegaly and demonstrated appropriate phasic and directional flow of the main portal vein, right portal vein, left portal vein, hepatic veins, and splenic vein.

Prednisone dose was decreased to 10 mg daily. Afterwards, she was followed every 3-4 months. Her last visit was on October 29, 2021. During this period, liver enzymes levels did not increase, albumin levels maintained remained normal, and bilirubin levels, prothrombin time, and partial thromboplastin time did not elevate. Vibration-controlled transient elastography was repeated in July 2019 and disclosed an increase in the mean liver stiffness score to 19.2 kPa. However, this score remained in the range of fibrosis stage 3, not progressing to stage 4 (cirrhotic liver). She did not require increasing prednisone dose above 10 mg daily.

Regarding her SLE, since she started taking milk thistle, her lupus remained clinically quiescent. She had no exacerbations or developed new clinical manifestations. In fact, leukopenia, which was previously present, resolved. Anti-dsDNA antibodies remained negative and C3 and C4 levels were normal.

Discussion

We describe a woman with SLE who developed AIH eight years after onset of lupus. Corticosteroid therapy was partially effective to control her AIH but induced several adverse effects. Treatments with azathioprine and mycophenolate mofetil also caused severe adverse events and were discontinued. Conversely, milk thistle therapy resulted in a favorable clinical response of her AIH, with normalization of liver enzymes and retarding the progression of her hepatic disease. Furthermore, it was effective to maintain her SLE controlled despite hydroxychloroquine being discontinued due to toxic maculopathy on the same year that milk thistle was started.

A liver biopsy was not performed in this patient, but this is not always necessary to establish the diagnosis of AIH. Based on simplified criteria for the diagnosis of autoimmune hepatitis, this patient had 6 points (2 points for ANA and/or SMA titers ≥1:80, 2 points for IgG levels >1.1 times the upper limit of normal, and 2 points for exclusion of viral hepatitis). The sensitivity and specificity for the diagnosis of AIH using a cutoff ≥6 for these criteria is 88% and 97%, respectively [6]. On the other hand, it is difficult to ascertain whether she had AIH associated with SLE (lupus hepatitis) or coexistent SLE and AIH. In general, it is very challenging to clearly establish these diagnostic possibilities even after careful evaluation of clinical, serologic, and histologic features [7].

Among complementary medicine alternatives for liver disease, Silybum marianum (milk thistle) is one of the best known and studied herbs. The active ingredient of Silybum marianum can be found in the seeds of the dried flower, also known as the bioflavonoid silymarin complex. The silymarin component with the greatest degree of biological activity is known as silibinin or silybin [8]. Milk thistle has been used for the treatment of several hepatic conditions including viral hepatitis, drug-induced liver injury, alcoholic liver disease, and nonalcoholic fatty liver disease [8-10]. It also seems to have clinical benefits for metabolic disorders, cardiovascular disease, and cancer [11-15].

The favorable clinical response to milk thistle observed in our patient was not surprising as silymarin is known to have a broad spectrum of functions including antioxidant, anti-inflammatory, and immunomodulatory effects [16-21]. Silymarin has been shown to raise glutathione levels in liver cells, a powerful antioxidant known as the front-line defense against the negative effects of free radicals [17]. It also exhibits significant anti-inflammatory activity by inhibiting 5-lipoxygenase activity [18]. The immunomodulatory and/or immunosuppressive activity of silymarin is exerted by a diverse range of mechanisms that include inhibition of NF-κB signaling pathway, TNF-α activation, T-lymphocyte function, Jun N-terminal kinase (JNK) activation, and apoptotic signaling, among others [17, 19-21].

Despite the known anti-inflammatory and immunomodulatory effects of milk thistle, there are no reports about its efficacy for AIH and autoimmune rheumatic diseases. There is only one publication in rheumatoid arthritis (RA) in which the T cells from patients with active RA and healthy controls were studied [22]. The investigators found that silybin induced apoptosis, decreased proliferation, and reduced the expression of IL-17 and TNF-α in T lymphocytes from patients and controls. In addition, silybin decreased the expression of microRNA-155, which has been shown to contribute to the immunopathogenesis of RA. Given the central role of T cells in the immunopathogenesis of both AIH and SLE, it is expected that milk thistle may have a positive impact in the treatment of these conditions [1, 23].

Milk thistle extracts are safe and may be used by a wide range of people, including breastfeeding mothers [24-25]. Silymarin has a good safety record as toxic or adverse effects seem to be minimal. Some gastrointestinal adverse events such as nausea and diarrhea may occur. Notably, only few mild drug inter-

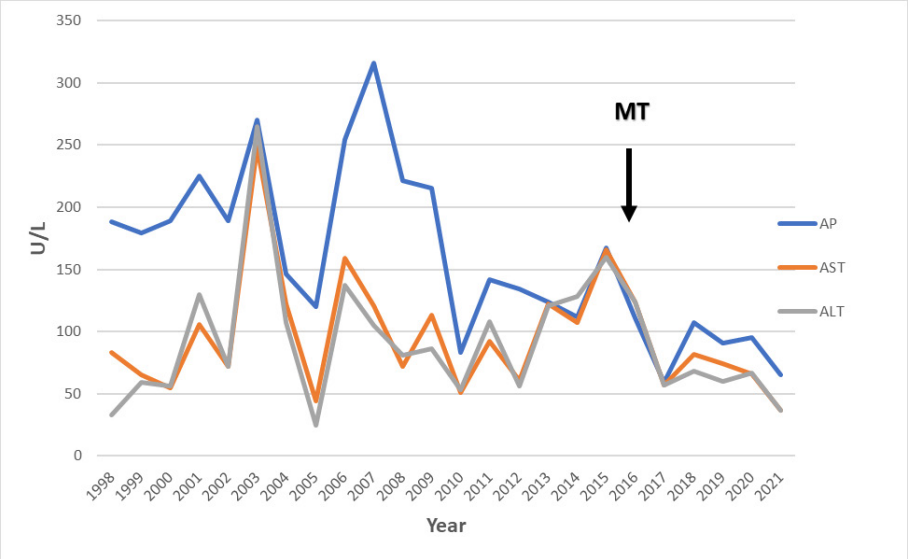

Figure 1: Trends of Alkaline Phosphatase (AP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels before and after Milk Thistle (MT) treatment.

actions have been reported and no significant effect on cytochrome P450 has been observed.

We must acknowledge that several studies have shown lack of efficacy of silymarin in chronic liver diseases. In a multicenter, double-blind, placebo-controlled trial conducted in patients with chronic hepatitis C infection who failed interferon-based therapy, silymarin did not significantly reduce serum ALT levels [26]. Moreover, a meta-analysis of randomized controlled trials of silymarin supplementation in patients with chronic hepatitis C showed no significant benefits on ALT levels and viral load [27]. In addition to the possible lack of efficacy of silymarin, serious concern exists regarding the composition of milk thistle. High-throughput analyses performed in 26 milk thistle-based dietary supplements revealed large differences in the silymarin content among these preparations that often differed from the information provided by the manufacturers [28].

To the best of our knowledge, this is the first report that demonstrates the clinical benefit of milk thistle both for AIH and SLE. Taken together, this report and the known immunomodulatory activity and favorable safety profile of milk thistle support the initiation of clinical studies as an adjunct therapy for its use in patients with autoimmune diseases.

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Author Contributions

All authors have participated sufficiently in this work to take responsibility for the work and to qualify as authors as by the ICMJE Criteria for Authorship. The following are the contributions for each author:

1. Substantial contribution to acquisition of data (Luis M. Vilá, MD)

2. Drafting the article or revising it critically for important intellectual content (Luis M. Vilá, MD and Lilifrancheska Lebrón-Torres, ND, MPH)

3. Final approval of the version of the article to be published (Luis M. Vilá, MD and Lilifrancheska Lebrón-Torres, ND, MPH)

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