Exacerbation of hemochromatosis by ingestion of milk thistle

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Milk thistle (*Silybum marianum)* is an herbal product commonly employed in treatment of liver conditions. In this case, milk thistle might have been responsible for exacerbating the clinical and biochemical presentation of C282Y homozygous hemochromatosis. Ceasing to ingest the milk thistle and removing only 2 g of iron by phlebotomy virtually normalized results of liver function tests and iron studies and eliminated this patient's clinical symptoms. Patients who have C282Y hemochromatosis should be cautious about taking milk thistle.

Case description

A 68-year-old Caucasian woman, presented with abnormal results of liver function tests, a ferritin level of 2118 µg/L (normal levels are 15 to 225 µg/L), and transferrin saturation of 98%. She complained of severe fatigue. Her body mass index was 33. Comorbid conditions included type 2 diabetes mellitus, asthma, hypothyroidism, borderline hypertension, borderline diastolic dysfunction, and a fatty liver diagnosed on ultrasound. She rarely consumed alcohol.

She had been ingesting milk thistle for more than a year in an attempt to improve her liver function. She was taking 1 pill a day (200 mg) of the Health Balance brand of milk thistle. Nonmedicinal ingredients in the milk thistle preparation were listed as sunflower oil, gelatin, purified water, glycerin, monoglycerides, lecithin, yellow beeswax, carob extract, and titanium dioxide. She also took a maximum of 2 extra-strength acetaminophen pills every 2 or 3 days and drank a can of cola every day.

Her liver function test results showed a γ-glutamyl transpeptidase (GT) level of 305 U/L (normal is <35 U/L), an alanine aminotransferase level of 56 U/L (normal is <36 U/L), and an aspartate aminotransferase level of 49 U/L (normal is <36 U/L). Results of tests for hepatitis B and C, HIV, and porphyria cutanea tarda were negative. Renal function, copper level, and α-fetoprotein tests were normal. Her hemoglobin (Hb) A_{1c} was 5.9% (normal is 4.8% to 6.2%).

High transferrin saturation often points to mutations in the HFE gene; HFE is the designation for the gene on the short arm of chromosome 6 that is associated with certain human leukocyte antigens and might be instrumental in iron or ferritin overload. Testing confirmed that the patient was homozygous for the C282Y mutation. Based on HFE test results, ferritin level, and transferrin saturation, she was diagnosed with hemochromatosis. Phlebotomy therapy was recommended. At this point, it was suggested that she discontinue the milk thistle, but she did not.

Deironing of 1 g of iron via 4 venesections resulted in a rapid fall in ferritin level, but γ-GT, alanine aminotransferase, and aspartate aminotransferase levels actually rose (**Table 1**). Consideration of a liver biopsy was postponed as her profile suggested nonalcoholic steatohepatitis (NASH). She was once again asked to discontinue the milk thistle.

She stopped taking the milk thistle and the moderate amounts of acetaminophen and cola she was ingesting. Her liver function and general well-being improved rapidly. After a total of 8 venesections of 500 mL each (equivalent to a total of 2 g of iron) her ferritin level had fallen to 141 µg/L, and results of her liver function tests were virtually normal. The venesections were done at approximate weekly intervals.

Discussion

PubMed was searched using the key words *hemochromatosis, milk thistle, nonalcoholic steatohepatitis,* and *drug-induced hepatitis.* Relevant articles and the proceedings of the 1st International BioIron Society Meeting in Prague in May 2005 were reviewed.

Milk thistle is held to be a treatment for liver disease, but this is controversial, and hepatotoxicity is possible.[1,2] No herbal medications have proven efficacy for treatment of C282Y homozygous hemochromatosis. The accepted treatment for hemochromatosis is venesection with the aim of reducing the ferritin level to 25 to 75 µg/L and maintaining it at that level.[3]

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Table 1. Patient's test results

TEST	4 MO BEFORE DIAGNOSIS	BEFORE VENESECTION	AFTER 4 VENESECTIONS OF 500 ML EACH	AFTER 8 VENESECTIONS OF 500 ML EACH
Ferritin, µg/L (Ref 15-225 µg/L)	Not known	2118	865	141
ϒ-Glutamyl transpeptidase, U/L (Ref <35 U/L)	123	305	500	64
Alanine aminotransferase, U/L (Ref <36 U/L)	29	56	63	27
Aspartate aminotransferase, U/L (Ref <36 U/L)	26	49	64	29
Hemoglobin A_{1c}, % (Ref 4.8% to 6.2%)	5.7	5.9	Not done	5.2

Ref—reference level.

γ-Glutamyl transpeptidase is not usually elevated in patients with C282Y homozygous hemochromatosis. Elevation of γ-GT suggests coexisting disease. The patient in this case had borderline diastolic dysfunction treated with furosemide, but she did not have congestive heart failure. Her cardiac status was stable during the treatment period. She was taking amitriptyline before she had the venesections, and she remained on the same dosage during treatment. It is unlikely that the elevated γ-GT was due to cardiac status or ingestion of antidepressants.

The possibility of NASH causing abnormal results of liver function tests was entertained. Diagnosis of NASH is consistent with the fatty liver seen on ultrasound. Overweight people and patients with diabetes are vulnerable to NASH. Treatment of NASH includes weight reduction, exercise, and discontinuation of any possible exacerbating medications.[4-6] This patient did not lose any weight during the time she was venesected of the 2 g of iron. She was able to begin walking again, but did not participate in any intensive exercise. Insulin resistance is associated with NASH, and uncontrolled diabetes is associated with elevated liver function results. This patient's liver dysfunction was unlikely to have been caused by decompensated diabetes as her HbA_{1c} was normal before phlebotomy. The HbA_{1c} level recorded after 8 venesections was also normal, but these results might have been inaccurate given the altered lifespan of the red blood cells due to venesection therapy.

Her fasting blood sugar at this time was 8.2 mmol/L (normal is 3.6 to 6.0 mmol/L), and she reported no deterioration or improvement in blood sugar levels on home testing. Clinically, her fatigue improved with venesection therapy and discontinuation of milk thistle.

A liver biopsy would likely have confirmed the diagnosis, but was not carried out because she improved substantially with venesection therapy and stopping the milk thistle. Drug-induced hepatitis often clears quickly upon withdrawal of the offending drug. Resolution of liver injury upon drug withdrawal is an important clue to etiology.[7,8]

Conclusion

This is the first description of a possible exacerbation of clinical and biochemical symptoms of C282Y homozygous hemochromatosis in a patient who ingested milk thistle for more than a year. Patients with C282Y homozygous hemochromatosis should be cautious about ingesting milk thistle in order to improve liver function, as it might have entirely the opposite effect.

EDITOR'S KEY POINTS

- The patient in this case was ingesting 1 pill a day (200 mg) of the Health Balance brand of milk thistle. Milk thistle, an herbal product, is held to be a treatment for liver disease, but this is controversial, and hepatotoxicity is a possibility.
- Based on hemochromatosis gene testing and assessment of her ferritin level and transferrin saturation, this patient was diagnosed with hemochromatosis.
- Ceasing to ingest the milk thistle and removing only 2 g of iron by phlebotomy virtually normalized results of her liver function tests and iron studies and eliminated her clinical symptoms.

POINTS DE REPÈRE DU RÉDACTEUR

- La patiente dans ce cas prenait un comprimé par jour (200 mg) de chardon-Marie de la marque Health Balance. On prétend que le chardon-Marie, une herbe médicinale, peut être utilisé dans le traitement des maladies du foie, mais c'est sujet à controverse et l'hépatotoxicité est une possibilité.
- En se fondant sur le dépistage génétique de l'hémochromatose et l'évaluation de son taux de ferritine et de saturation de transferrine, on a diagnostiqué l'hémochromatose chez cette patiente.
- En arrêtant de prendre du chardon-Marie et en lui enlevant seulement 2 g de fer par phlébotomie, les résultats des tests de sa fonction hépatique et ses taux de fer sont revenus presque à la normale, et ses symptômes cliniques ont disparu.

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Competing interests

None declared

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References

1. Crocenzi FA, Roma MG. Silymarin as a new hepatoprotective agent in experimental cholestasis: new possibilities for an ancient medication. *Curr Med Chem* 2006;13(9):1055-74.
2. Rambaldi A, Jacobs BP, Iaquinto G, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases—a systematic Cochrane hepato-biliary group review with meta-analyses of randomized trials. *Am J Gastroenterol* 2005;100(11):2583-91.
3. Proceedings of the 1st International BioIron Society Meeting, Prague, Czech Republic, May 22-27, 2005.
4. Marchesini G, Babini M. Nonalcoholic fatty liver disease and the metabolic syndrome. *Minerva Cardioangiol* 2006;54(2):229-39.
5. Yoneda M, Fujita K, Iwasaki T, Maeyama S, Terauchi Y, Nakajima A. Treatment of NASH: nutritional counseling and physical exercise. *Nippon Rinsho* 2006;64(6):1139-45.
6. Sreenivasa Baba C, Alexander G, Kalyani B, Pandey R, Rastogi S, Pandey A, et al. Effect of exercise and dietary modification on serum aminotransferase levels in patients with nonalcoholic steatohepatitis. *J Gastroenterol Hepatol* 2006;21(1 Pt 1):191-8.
7. Yuce B, Gulberg V, Diebold J, Gerbes AL. Hepatitis induced by Noni juice from Morinda citrifolia: a rare cause of hepatotoxicity or the tip of the iceberg? *Digestion* 2006;73(2-3):167-70.
8. Furbee RB, Barlotta KS, Allen MK, Holstege CP. Hepatotoxicity associated with herbal products. *Clin Lab Med* 2006;26(1):227-41.