International Journal of Research in Medical Sciences
Abousherif W et al. Int J Res Med Sci. 2022 Aug;10(8):1766-1768
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20221992

Case Report

Recurrent bilateral superficial vein thrombosis in hereditary hemochromatosis- a case report

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Received: 24 June 2022
Revised: 13 July 2022
Accepted: 18 July 2022

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ABSTRACT

We report a rare case of recurrent bilateral superficial vein thrombosis (SVT) in a 45-year-old former smoking male with hereditary hemochromatosis on anticoagulation therapy with unremarkable hypercoagulable workup. This case report adds to the growing evidence that hemochromatosis is one of the rare causes of recurrent SVT, and thrombosis can still occur despite full-dose anticoagulation. Future studies assessing optimal management of the recurrent SVT in hemochromatosis patients are warranted.

Keywords: Hemochromatosis, Superficial vein thrombosis, Thrombosis

INTRODUCTION

Hereditary hemochromatosis is the most common autosomal recessive disorder with a prevalence of 1 case in 200-500 individuals in the United States and is mostly observed among people of northern European origin.[1] It is characterized by disruption in iron homeostasis, which leads to iron overload systematically and multiple organ dysfunction.[2,3] Several studies have reported an association between hemochromatosis and cardiovascular events and acute portal vein thrombosis possibly due to excess accumulation of iron.[4-8] Here we report a case of recurrent bilateral superficial thrombosis in a middle-aged male with hemochromatosis on anticoagulation therapy.

CASE REPORT

A 45-year-old former smoking male initially presented four years prior with pathologic fractures and was found to have osteopenia on a bone density scan with T-scores ranging between -1.1 to -2.0 standard deviation (SD). Serum and urine protein electrophoresis were negative for protein spikes. 25-hydroxyvitamin D was 32 ng/ml. Parathyroid hormone (PTH) was 39.7 pg/ml. Iron panel was abnormal with iron level 177 ug/dl (45-160), saturated iron 81% (20-50%), total iron-binding capacity (TIBC) 218 ug/dl (250-450), transferrin 147 mg/dl (200-375), and ferritin 400 ng/ml (20-300). Bioavailable testosterone was low 90.2 ng/dl (110-575). Left ventricular ejection fraction was estimated 35-40% (normal 60%). He underwent genetic testing which revealed a mutation in p.C282Y and was diagnosed with hereditary hemochromatosis. He was treated with phlebotomy as needed to achieve a goal of ferritin below 50 and iron saturation below 50%. Liver fibroscan was negative for fibrosis. His ejection fraction improved to 60% on repeat echocardiogram after two years.

Two years after his diagnosis of hemochromatosis, he developed calf pain and ankle swelling for which a venous ultrasound revealed bilateral superficial vein thrombosis (SVT) in the short saphenous vein (SSV) with no evidence

of deep vein thrombosis. He was started on apixaban 5 mg twice daily for 45 days. Repeat ultrasound revealed superficial thrombophlebitis in the bilateral SSV with associated reflux. After completing apixaban therapy he underwent a hypercoagulable workup which revealed normal prothrombin time (PT), activated partial thromboplastin time (aPTT), diluted Russell viper venom test (DRVVT), hexagonal phospholipid neutralization, factor 5 Leiden, cardiolipin antibody, beta-2 glycoprotein antibodies, antithrombin III, protein C, and protein S.

He continued to have symptoms despite restarting apixaban, so he underwent endovenous laser therapy of the right short saphenous vein with improvement in his pain and swelling. One year later he had a recurrence of his calf pain which he described as the same as the pain when he was first diagnosed with SVT. Venous ultrasound revealed recurrence of bilateral SSV SVT. He was compliant with compression stockings as well as anticoagulation and denied ever missing a dose. His apixaban was increased to 10 mg BID for 7 days followed by 5 mg BID indefinitely.

Table 1: Laboratory data.

Parameters	Values
25-hydroxy vitamin D	32
PTH	39.7
Iron	177*
Saturated iron	81*
Transferrin	147
Ferritin	400*
Testosterone	90.2*
Total iron-binding capacity (TIBC)	218

*Abnormal values

DISCUSSION

Hemochromatosis is a disorder characterized by excess systemic iron deposition and, in turn, multiple organ dysfunction.[9,10]

Hereditary hemochromatosis is diagnosed in patients who are homozygotes with a hemochromatosis gene (HFE) protein mutation.[11] This mutation results in enhanced iron absorption independent of a normal dietary iron intake. The most common mutations in this gene are C282Y and H63D which are found on the short arm of chromosome 6.[12] In addition, environmental and genetic modifying factors are recognized.[9]

The mechanism of how excess iron levels can accelerate thrombosis is not fully understood. Previous studies have suggested that accelerated thrombosis may be due to impaired vasoreactivity, and enhanced production of reactive oxygen species and systemic markers of oxidative stress.[13] Moreover, there is evidence that HFE C282Y could interact with other predisposing factors for venous thromboembolism, such as factor V Leiden, thus exacerbating their prothrombotic effect.[8,14] In our patient, the coagulopathy screen was unremarkable.

Management of recurrent superficial vein thrombosis in hemochromatosis is not well established. In a meta-analysis of phase III trials investigating the efficacy and safety of the new oral anticoagulants (NOAs) in the management of VTE, by including 10 randomized control trials with approximately 38,000 patients, Kakkos and colleagues concluded that compared to vitamin K antagonists, NOAs are effective in the treatment of VTE and offer plausible safety profile in terms of bleeding.[15] Similarly, our patient was started on apixaban 5 mg BID initially and due to recurrence of SVTs, the dose of apixaban was increased to 10 mg BID for 7 days followed by 5 mg BID indefinitely. Future studies assessing optimal management of the recurrent SVT in hemochromatosis patients are warranted.

CONCLUSION

The present case raises concerns about the association between hemochromatosis and iron overload and recurrent thrombotic events in these patients despite standard management.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Abousherif W, Vameghestahbanati M, Hallak A. Recurrent bilateral superficial vein thrombosis in hereditary hemochromatosis- a case report. Int J Res Med Sci 2022;10:1766-8.