JACOBS PUBLISHERS

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Jacobs Journal of Hematology

Case Report

Botanic Selective Estrogen Receptor Modulators (SERMs) and Venous Thrombo Emboli (VTE)

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Received: 09-10-2015

Accepted: 09-24-2015

Published: 09-29-2015

Abstract

Objective

Estrogens are widely used as relieving agents for women suffering from postmenopausal symptoms. In order to prevent side effects of estrogens (breast or uterine cancer) and promote desirable effects (preventing osteoporosis and atherosclerosis) selective estrogenic receptor modulators [SERM's] were developed. Botanical SERMs are considered beneficial and safe. We would like to describe a 56 years old woman who got a botanic SERM (marketed as an over the counter food supplement) and was admitted with fever and occlusion of the portal venous system.

Methods

Clinical follow up, an abdominal CT, a serological work-up of viruses and possible infectious agents. Screening her thrombophilia panel and clotting systems.

Results

She had an acute CMV (IgM) infection, was found to be heterogenous to MTHFR C677T deficiency, had protein C deficiency and a positive lupus anticoagulant. After treating with Warfarin the portal vein thrombus was gone and there were no signs of portal hypertension.

Conclusions

Botanical SERMs are widely used as post-menopausal food supplements with the assumption that they are safe. We recommend screening of the thrombophilia panel before using botanical SERMs for postmenopausal women.

Keywords: SERMs; MTHFR deficiency; protein C deficiency; APLA

Abbreviations

LRV – left renal vein;

PV – portal vein;

SMV – superior mesenteric vein

Background

Estrogens medications are widely used as an adjuvant treatment for breast cancer and as relieving agents for women suffering from postmenopausal symptoms. They act by binding to DNA and modulate the transcription rate of specific genes [1]. In order to prevent undesired side effects of estrogen (such as breast or uterine cancer) and promote desirable affects such as preventing osteoporosis and atherosclerosis [2], new estrogenic compounds, which affect estrogenic receptors on selected sites [SERM's], were developed. Botanic SERMs are considered beneficial and safe [1]. We would like to describe a 56 years old woman who took a botanic SERM to control her menopausal symptoms and was admitted with fever and weakness.

Patient Description

A 56 year old white woman was admitted to our hospital with a flu-like infection, which she claimed started a week ago. She had been taking Femarelle (a botanic SERM that can be purchased over the counter as a food additive, 1 capsule a day on a daily basis for almost 1 year. She had no other complaints, and her physical examination showed that she was completely normal. Her past medical history was clear without any thromboembolic events (VTE) ever (including during pregnancies), did not have spontaneous abortions, and had no family history of VTE. Chest and sinus x-rays were normal, as were her hematological lab results. However, her liver tests (AST 618, ALT 710, LDH 1922, Ferritin 1500, and CRP 59) demonstrated dysfunction of the liver. In an abdominal ultrasound, a thrombus (1.0x1.6 cm) in the portal vein, that was suspected to be a blood clot, was observed. In an abdominal CT scan, a thrombus was discovered that was infiltrating from the portal vein into the left renal vein, the inferior mesenteric vein and the left ovarian vein (Figure 1).

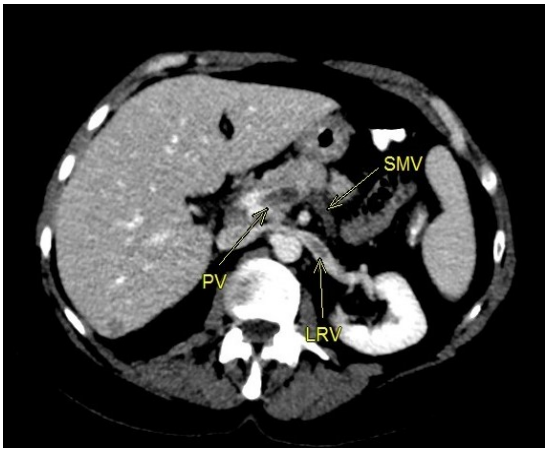

Figure 1

The chest CT angiography and venous duplex ultrasound of the lower limbs were normal, without any evidence of thrombosis. Her thrombophilia profile indicated that she was heterozygous for the MTHFR C677T mutation, had protein C deficiency and a positive lupus anticoagulant (LAC). Factor V Leiden mutation and Prothrombin IgG) were normal. Viral serology panel found that she had a positive CMV infection (IgM). She was treated with Coumadin (INR > 2) for 3 months. A follow up abdominal CT found no evidence of thrombi.

Discussion

Femarelle is a SERM derived from a botanical source containing DT56a. Several studies have shown data defining the safety profile and clinical efficacy of DT56a. It has been shown to alleviate menopausal symptoms, particularly relieving vasomotor symptoms [2], with no effect on the endometrium or the sex steroid blood level. A recent study concluded that Femarelle does not adversely affect platelet reactivity as measured by PFA closure times in symptomatic thrombophilic postmenopausal women or normal controls, and so may offer a new clinical choice for therapy of symptomatic postmenopausal women [3-4]. Our patient was found to be heterozygous to MTHFR C677T mutation, had protein C deficiency and lupus anticoagulant (LAC). She was using Femarelle as a food additive, without understanding its possible harmful effect, as SERMs could have some dangerous effects as potential pro-atherogenic substances for patients at risk – mainly with thrombophilia [2].

The thrombus in the venous system that was found in this patient could be related to the acute infection with CMV (known to cause thromboembolic events) altogether with her genetic traits (MTHFR deficiency, protein C deficiency and APLA) – all contributed the higher danger to trigger a thrombus formation while receiving a SERM. SERMs were designed to prevent the malignant effects of estrogen on the breast and the endometrium, but do not prevent thromboembolic events. Epidemiological observations, clinical studies, and basic laboratory research suggested that estrogen replacement therapy is associated with beneficial cardiovascular effects in postmenopausal women. Estrogen has a multitude of biological effects that may account for this apparent benefit (which remain to be proven in randomized clinical trials), including favorable effects on the lipid profile, a direct effect on the vascular endothelium with increased nitric oxide bioactivity, and improved fibrinolysis. However, long-term oestrogen therapy increases the risk of breast and endometrial cancers. Selective estrogen receptor modulator, producing estrogen-agonistic effects in some tissues (liver, bone), and estrogen-antagonistic effects in others (breast, uterus), and may prove to be an option for women with atherosclerosis and its associated risk factors who might benefit from estrogen therapy [5].

Matrix metalloproteinases (MMPs), proteolytic enzymes produced by monocytes, may contribute to atherosclerotic arte-

rial wall remodeling and to plaque rupture. Because estrogen influences the synthesis of MMPs the effect of raloxifene (a selective estrogen receptor modulator) on monocyte MMP production was studied. Human primary blood monocytes treated with raloxifene (10 micromol/L) in the presence of lipopolysaccharide (LPS) or tumor necrosis factor-alpha and granulocyte-macrophage colony-stimulating factor induced a 2- to 3-fold increase in MMP-1 production by monocytes. The enhancement of MMP-1 production by raloxifene in LPS-activated monocytes occurred through a cyclooxygenase-2- and prostaglandin E(2)-independent mechanism. Additionally, compared with monocytes acquired during the placebo phase, peripheral blood monocytes from 5 of 6 healthy postmenopausal women treated with raloxifene (60 mg daily for 1 month) in a clinical trial produced significantly higher levels of MMP-1 when the monocytes were activated with LPS. Furthermore, serum obtained during the raloxifene phase from 4 of these subjects, when added to control monocytes, significantly enhanced LPS-induced MMP-1 production compared with that from serum obtained during the placebo phase. In summary, raloxifene increased the production of MMP-1 in activated monocytes; this effect may be favorable in atherosclerotic arterial wall remodeling but unfavorable for plaque stability [6].

Femarrelle has a safety reputation and can be purchased over the counter without a prescription, however, our case demonstrated that natural botanic substances are not entirely safe and some precautions should be applied before taking these natural substances.

Conclusions

As SERMs are widely used as postmenopausal medications with the assumption that they are “natural and harmless”, we recommend studying the thrombophilia profile and coagulation factors deficiency before using SERMs. We suggest to limit the free access to SERMs and to consider them as prescription medications and not as food additives that can be purchased without any precautions.

Disclosure

None, for all authors

Funding

None

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