Case Report

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Spinal and cerebral hematoma in systemic lupus erythematosus and antiphospholipid syndrome: is drug interaction the culprit?

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Abstract

Objectives: Thrombotic events are common in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). Warfarin is the most commonly used anticoagulant drug for thrombosis treatment, but it can interact with many drugs, foods, or medicinal herbs. Herein, we presented a case with SLE and APS who was complicated by spinal and cerebral hematoma as a result of warfarin interaction.

Case presentation: Spinal subdural hematoma and frontal intraparenchymal hematoma were occurred in our patient, who was in remission for 2 years with rituximab, hydroxychloroquine and warfarin. We learned that she had been using some herbal products (shepherd's purse and horsetail) and phenylramidol for a few days. Spinal and cerebral hematomas caused by the interaction of phenylramidol and warfarin were treated with fresh frozen plasma and vitamin K without the need for surgery.

Conclusions: The drug interactions with warfarin can cause fatal hemorrhagic or thrombotic events. Especially, the patients with SLE and/or APS using warfarin should be warned not to use different medications or herbal agents.

Introduction

Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are two frequently associated diseases that mostly affect women of childbearing age [1]. Clearly, both diseases are a risk factor for arterial and/or venous thrombotic events [2]. Antiphospholipid antibodies (aPLs) have been identified in approximately 50% of SLE patients [3]. According to current guidelines, the thrombosis treatment in SLE patients with aPL is the use of vitamin K antagonists (VKA), even if they do not complete APS criteria [4].

Warfarin is the most commonly used VKA for long-term anticoagulation therapy, but it requires frequent laboratory monitoring and dose adjustment [5]. Warfarin is among the medicines with the highest incidence of medicine-related life-threatening events and tops the list of interactions with foods, herbal agents, and drugs. Interactions resulting in excessive or insufficient anticoagulation highly augment the risk of fetal bleeding or thrombotic events [6].

Herein, we report a patient with SLE associated APS presenting spinal and cerebral hematoma who used herbal supplements and phenylramidol combination with warfarin after the rituximab (RTX) therapy.

Case presentation

In July 2010, a 25-year-old female was admitted to our outpatient clinic with necrotic sores on the distal tibial zone for three months. When she was hospitalized, there was a soft tissue defect (10 × 12 cm at size) on the right distal medial tibia. The results of the laboratory tests were as follows; lymphopenia (900 per mm³), mild thrombocytopenia (132 × 10³/μL), anti-nuclear antibodies 1:1,000 granular, extractable nuclear antigen were positive

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(anti-SSA: 206 RU/mL), elevated anti-dsDNA and positive aPLs (lupus anticoagulant and anticardiolipin Ig G), increased erythrocyte sedimentation rate 84 mm/h (0–20 mm/h) and C-reactive protein 1.22 mg/dL (0–0.8 mg/dL). For her necrotic sores, peripheral arterial computed tomography (CT) angiography was performed and it was revealed the occlusion of distal right anterior tibial artery and proximal left posterior tibial artery. During follow-up, edema on her face and neck, shortness of breath, and tachypnea were added to the clinical picture. Pulmonary and neck CT-angiography showed a thrombus in the superior vena cava and the right inferior pulmonary artery. In July 2010, with the diagnosis of SLE associated APS, enoxaparin sodium plus low-dose aspirin (LDA), prednisolone 60 mg/day (after pulse steroid) with dose reduction scheme, hydroxychloroquine (HCQ) and cyclophosphamide (CYC) were started. After six doses of CYC were given monthly, maintenance therapy was continued with azathioprine (AZA) (150 mg/day), HCQ (400 mg/day) and low dose prednisolone in addition to warfarin plus LDA. She was followed with these medications for seven years.

In August 2018, she returned to the emergency department with edema on her face, neck, and lower extremities. In the anamnesis of the patient, we learned that she had two pregnancy losses one year ago and three months ago. We hospitalized her again with flare of the disease. The doppler ultrasonography was not visualized the right jugular vein due to totally thrombosis. In physical examination, she had grade 2 pitting edema on legs and her urine protein level was 6 gr/day. Additionally, her

creatinine level was 2.5 mg/dL (baseline renal function tests were normal). The treatment was given after plasma exchange as intravenous immunoglobulin (IVIG) for five days, prednisolone 60 mg/day (after pulse steroid) and added RTX 1 g on the first and fifteenth day. She was discharged with RTX every six months, 60 mg/day prednisolone with dose reduction scheme, HCQ (400 mg/day) and warfarin plus LDA.

In January 2020, she was admitted to the emergency department with widespread myalgia, bruising on various parts of the body, and difficulty walking which lasted for four days. The international normalized ratio (INR) was 11. She did not have gastrointestinal bleeding symptoms, hemoptysis, headache, and confusion. In physical examination, there were various hematomas on her body that the largest one was 10 × 20 cm on the forearm. Warfarin and LDA were held immediately and different medicines or herbal products were investigated whether she used. We learned that she had been drinking shepherd's purse (*Capsella bursa*) and horsetail (*Equisetum arvense*) tea for two weeks. Additionally, she used to receive phenylramidol for low back pain for a few days. After vitamin K 10 mg and fresh frozen plasma were given for decreasing INR, we contacted clinical pharmacist to learn about the herbal products and phenylramidol and their interaction with warfarin. The clinical pharmacist told that herbal agents used by the patient did not interact with warfarin, but phenylramidol would be able to do this interaction.

Spinal and cerebral imaging was performed to the patient with difficulty walking and low back pain. Spinal

Figure 1: Subdural hematoma with the spinal cord and cauda equina compression. The sagittal T1-weighted (W) image (A) shows hyperintense subacute extramedullary hematoma (arrows) extending from the level of C5 vertebra to the distal spinal canal. Axial T1W (B) and T2W (C) images at the level of T6 vertebra reveal intrathecal-subdural location of hematoma (arrows) displacing the spinal cord (curved arrow) anteriorly and slightly to the right. Axial T1W (D) image at the level of L4 vertebra shows compression of cauda equina fibers (thick arrows) by subdural hematoma.

Figure 2: Cerebral subdural and parenchymal hematoma. The axial T2W (A) and T1W (B) images show early subacute parenchymal hematoma (thin arrows) with associated peripheral white matter edema (thick arrow) at the left frontal lobe. The axial fluid attenuated inversion recovery (FLAIR) image (C) also shows punctate chronic ischemic lesions (circles) in bilateral cerebral deep white matter. Please note associated thin subdural hematoma adjacent to the left frontal parenchymal hematoma (arrowheads).

magnetic resonance imaging (MRI) detected subacute subdural hematoma with predominant posterior location, extending from the level of C5 vertebra to the distal spinal canal (Figure 1). Although there was an apparent compression on spinal cord and cauda equina fibers at images, she had no sensory and motor deficit in neurological examination. Brain MRI showed a 2 × 2 cm frontal parenchymal hematoma on the left hemisphere with adjacent thin subdural hematoma (Figure 2). The operation for hematoma was not planned by neurosurgeons because of her neurological examination was normal. Absolute bed rest and neurological examination follow-up were suggested hourly. Both her low back pain, headache, bruising on the body decreased and walking improved in clinical follow-up. After the INR level dropped below two, enoxaparin sodium was started for secondary prophylaxis of thrombosis. Finally, the patient was discharged with a date of control spinal and cranial MRI for six weeks later.

Ethical approval and informed consent: All methods completed in the studies including human participants were in compliance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The patient was informed and a written consent was obtained for the case report.

Discussion

SLE and APS are two frequently associated diseases that occur a risk for arterial and/or venous thrombotic events [1]. It is anticipated that up to 50–70% of SLE patients with aPL may evolve APS after 20 years of follow-up [2]. aPLs have been identified in approximately 50% of SLE patients. In this clinical picture, life-threatening attacks may occur as occlusive arterial and/or venous thrombotic events or pregnancy complication (preeclampsia, HELLP Syndrome)

[7, 8]. Similarly, the development of vena cava superior syndrome and pulmonary artery thrombosis are life-threatening conditions in our patient.

The life-threatening conditions in SLE-associated APS patients require immunosuppressive therapy together thromboprophylaxis for long-term remission [9]. Glucocorticoids, CYC, RTX, mycophenolate mofetil (MMF), and AZA are the main immunosuppressive agents prescribed in these patients for disease activity control [9, 10]. Our case was followed in remission with AZA and HCQ for seven years after induction therapy with CYC and corticosteroid. After seven years of remission, RTX was used for the disease flare in our patient.

In conclusive APS (primary or associated-SLE) patients with first venous thrombosis, INR 2.0–3.0 is proposed using VKA while INR > 3.0 or INR 2.0–3.0 plus LDA (100 mg/daily) are suggested for arterial thrombotic events [4]. Patients with recurrent venous thrombosis during VKA treatment should be treated with a higher INR range (>3.0) or with the combination anticoagulant-antiaggregant [11]. Our case received warfarin and LDA due to previous arterial thrombus and recurrent venous thrombus.

Warfarin has the capacity to interact with many medicines, herbal agents, and food, which raises the risk of adverse events [6]. Herbs-drug interactions involve primarily inhibition or induction of cytochrome P450 enzymes [12]. The usage of warfarin with herbs is a standard example of pharmacodynamic interactions. Anticoagulant effects of warfarin could increase when it is administered concomitantly with coumarin containing herbs or with antiplatelet herbs [6].

Based on limited literature knowledge it has been determined that herbal products, *C. bursa-pastoris* (shepherd's purse) and horsetail used by our patient, increase platelet aggregation and are used in bleeding control [13, 14]. In a randomized controlled trial, hydroalcoholic extracts of *C. bursa-pastoris* capsule were demonstrated to

be effective in reducing menstrual bleeding [15]. In contrast to the herbal agents used by our patient, some Moroccan medicinal plants showed thrombocyte antiaggregant properties with dose-dependent inhibition of thrombin and ADP-induced aggregation [16]. The clinical results of drug interaction are attached to many factors, such as co-administered drugs, comorbidities of the patients, the structure of the herbal product, and the received dosage regimens [12].

On the other hand, the patient had used phenylramidol when she was taking warfarin. Phenylramidol is a non-narcotic analgesic drug with concomitant muscle-relaxant activity. It is conjugated with glucuronic acid in the liver and excreted in the urine as the form of phenylramidol glucuronide [17]. To our knowledge, warfarin is mainly metabolized in the liver with the enzyme CYP2C9. Other minor enzymes are CYP 2C19 and CYP3A4. Phenylramidol interaction with warfarin is based on the inhibition of CYC 2C9, the enzyme responsible for warfarin metabolism, by phenylramidol [18]. In the literature, it was reported that the addition of fenylramidol to patients using anticoagulant therapy in two cases caused excessive hypoprothrombinemia and developed diffuse hemorrhagic symptoms. Therefore, administration of phenylramidol to patients who receive anticoagulant therapy is dangerous unless special precautions are taken [19].

Consequently, warfarin can interact with many drugs, foods, or herbal products. As a result of this interaction, fatal bleeding or recurrent thrombosis may occur. In particular, patients with SLE and/or APS using warfarin should be cautioned not to use different medications or herbal agents.

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