CLINICAL VIGNETTE

An Uncommon Risk of Vaginal Estrogen Therapy

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Clinical Case

A 71-year-old woman presents to the Emergency Department complaining of worsening dyspnea on exertion. For the past several months, she noticed gradually worsening dyspnea on exertion. She normally walks 2 miles daily without any issues. She now reports shortness of breath walking 1 block. On the morning of presentation, she noticed new mild chest pressure with walking. She also reports 15-pound weight gain over past few months and occasional cough productive of clear sputum, usually in the mornings and mild intermittent wheezing. She denies any fevers, chills, sore throat, nasal congestion, rhinorrhea, nausea, vomiting, diarrhea, orthopnea or lower extremity edema. She denies any recent travel and received both doses of her initial COVID-19 vaccine. Her past medical history is significant for obstructive sleep apnea on nightly CPAP, osteoporosis, trigeminal neuralgia s/p decompression surgery, hyperlipidemia, prediabetes and recurrent urinary tract infections. Her father had coronary artery disease in his 70s. Her medications include gabapentin 600 mg 3 times daily, calcium/vitamin D supplement, vitamin B12 supplement, Estradiol 10 mcg tablet twice weekly and nasal fluticasone as needed. She is married and lives with her husband. She is a retired x-ray technician with remote history of smoking cigarettes from age 18-30, averaging 1 pack per day. She drinks 2 glasses of wine per week.

The patient's exam revealed elevated blood pressure of 159/86, elevated pulse of 105, temperature 36.6 degrees Celsius and oxygen saturation slightly low at 92% on room air. Pertinent exam findings included a comfortable appearing woman without acute distress, with moist mucus membranes, clear oropharynx and nasal turbinates. Lungs were clear to auscultation bilaterally, without rales or wheezing. She was slightly tachycardic with regular rhythm, symmetric distal pulses and trace bipedal edema symmetrically.

The patient was started on 2 liters oxygen via nasal cannula for low oxygen saturation. EKG showed sinus tachycardia. Labs included revealed negative troponins x 2, normal BNP, normal metabolic panel, complete blood count and urinalysis. Chest x-ray showed mild biapical distortion of lung parenchymal pleural interface consistent with chronic post inflammatory change. Lungs were otherwise unremarkable. D-dimer was elevated at 1.88 ug/mL and a CT Chest showed bilateral large volume pulmonary emboli with mildly enlarged main pulmonary arteries. Ultrasound of lower extremities showed no deep vein thromboses bilaterally. Echocardiogram showed normal LVEF 55-60% with mild diastolic dysfunction. There was no evidence of right ventricular strain or significant valvular dysfunction.

This patient's worsening dyspnea on exertion and chest pressure was due to acute bilateral pulmonary emboli. She was started on a heparin drip, and transitioned to apixaban with loading dose. She was weaned off supplemental oxygen and discharged home in stable condition.

The cause for her bilateral pulmonary emboli was unclear. She had no history of cancers, immobility, recent surgery or a personal or family history of thrombotic events. She was seen by a hematologist before discharge. Hypercoagulable testing including, cardiolipin antibodies, beta-2 glycoprotein, prothrombin gene mutation, Factor V Leiden and JAK-2 mutation analysis which were all unrevealing. The current plan is to continue with apixaban for a total of 6 months. The hematologist felt the most likely cause for the pulmonary emboli was vaginal estrogen therapy which was started 3 months prior to presentation for treatment of recurrent urinary tract infections. Her Estradiol tablet was discontinued, and she developed another urinary tract infection soon after.

Discussion

Many women complain of post-menopausal vulvovaginal symptoms, including vaginal dryness, burning and dyspareunia. In addition, urinary frequency and recurrent bladder infections are also common.[1] The loss of estrogen that occurs with menopause causes the atrophic symptoms in the vulvovaginal and bladder-urethral areas. Some of the more troublesome and persistent issues that can occur post-menopause include sexual dysfunction, post-coital bleeding and recurrent urinary tract infections.[1] Many women opt to pursue non-hormonal or hormonal therapy to help alleviate these symptoms. First-line treatments for post-menopause vaginal symptoms including dryness, burning and dyspareunia are non-hormonal vaginal moisturizers and lubricants.[2] Unfortunately, these often do not provide adequate relief so, estrogen-based therapy is necessary. Vaginal estrogen therapy is an effective treatment for symptoms of vulvovaginal dryness such as burning or itching, postcoital bleeding or dyspareunia.[1] It can also improve urinary tract symptoms such as urinary frequency and recurrent urinary tract infections, in addition to the vaginal symptoms. However, it has not been shown to be effective in treating urinary incon-

tinence.[1] It is considered appropriate to use estrogen therapy for patients who have symptoms of vaginal atrophy with low serum estrogen levels as long as there is no contraindication history of estrogen-dependent cancers.[2]

There are several preparations of vaginal estrogen therapy available including estradiol cream, tablet, capsule and ring. Systematic reviews have found that creams, tablets and rings are equally effective in alleviating symptoms of vaginal atrophy. Vaginal estrogen therapy works by restoring the normal vaginal acidic pH and microflora, thereby thickening the vaginal epithelium and increasing vaginal secretions, resulting in decreased vaginal dryness. Vaginal estrogen therapy is widely considered to be very safe with uncommon adverse effects. Some patients can complain of vaginal irritation, vaginal bleeding or breast tenderness with vaginal estrogen therapy.[3]

The vaginal estrogen preparations considered to have the lowest systemic absorption are the tablet or capsule at 4 mcg or 10 mcg formulations and the estradiol ring at 7.5 mcg/day. The term low-dose vaginal estrogen is defined by < or = 50 mcg serum estradiol. Theoretically, low dose vaginal estrogen preparations do not require concomitant use of opposing progesterone therapy since endometrial proliferation is not anticipated. The serum absorption of vaginal estrogen therapy at recommended doses is less than oral or transdermal estrogen therapy.[4] The serum estradiol levels found with low dose vaginal estrogen therapy is slightly higher than the average level for postmenopausal patients, averaging about 5 pg/mL. Some studies have shown that the systemic absorption of vaginal estrogen therapy is about 30% lower than levels found with the same dose of oral estrogen therapy.[5] It is unclear if the severity of vaginal atrophy can affect the systemic absorption of estrogen. Some report systemic absorption of estrogen is highest in the first days or weeks of initiating therapy, and then decreases over time with ongoing use. This is supported by the idea that absorption of estrogen through thin atrophic vaginal epithelium is highest with initiation of therapy when the vaginal lining is thinnest.[6] There are no reports that have linked vaginal estrogen therapy with the risk of clot formation such as deep vein thrombosis or pulmonary emboli. However, given the slight increase of serum estradiol concentration, particularly with initiation of therapy, there is a possible risk for a thromboembolic event.

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