



Letter

Angioedema attacks related to endometrial hyperplasia in a case of estrogen-dependent factor XII hereditary angioedema

Hereditary angioedema (HAE) with normal C1-esterase inhibitor (C1-INH) is characterized by recurrent skin or mucosal angioedema attacks, lack of urticaria, and nonresponsiveness to antihistamines and corticosteroids, affecting mainly women with family history of angioedema and no C1-INH abnormalities.^{1–3} Missense mutations in the coagulation factor XII (FXII) gene (mainly Thr328Lys and Thr328Arg) have been associated with this type of HAE, causing an increase in FXII activity and leading to enhanced bradykinin production.^{4–6} Angioedema attacks may be exclusively related to or influenced by hyperestrogenic situations, such as pregnancy or exogenous estrogen exposure, in women taking estrogen-containing oral contraceptives or receiving hormonal replacement therapy.^{1,3,7,8} There are no reports in the literature relating this condition to endometrial hyperplasia (EH).

A 43-year old woman was diagnosed with FXII-HAE in 2006 at the age of 35 years during her first pregnancy. She began experiencing recurrent angioedema attacks, with peripheral, facial, abdominal, and laryngeal locations, that lasted 10 to 48 hours. Treatment with antihistamines and corticosteroids at the emergency department was not effective. C4-inhibitor and C1-INH levels and function were within the normal range. Her grandmother and her mother also developed angioedema attacks during pregnancies. Her sister presented with 2 episodes of angioedema while taking estrogen-containing oral contraceptives. Thr328Lys mutation in the *FXII* gene was detected in the patient and her mother, sister, and son. She did not receive any specific treatment during pregnancy. Angioedema episodes ceased after delivery. She avoided exogenous estrogen exposure and angiotensin-converting enzyme inhibitors and had no more pregnancies, remaining asymptomatic.

In 2015, the patient was diagnosed with EH without atypia, and her gynecologist consulted us to start treatment with progestin. At the same time, on March 23, she experienced an episode of feet swelling followed by intense acute abdominal pain with nausea and vomiting. Abdominal pain lasted for 8 hours and feet swelling for 36 hours with no specific treatment. C1-INH concentrate and ica-tibant acetate were then provided as on-demand therapy, and she was trained in self-administration at home. On April 1, oral medroxyprogesterone acetate was prescribed (10 mg/d for 12 days from day 14 of every menstrual cycle). She experienced swelling of one finger that lasted for approximately 10 hours the same day she started treatment and an abdominal attack that lasted 18 hours after a first cycle of medroxyprogesterone treatment. She completed a total of 7 cycles of medroxyprogesterone until September 2015, with no further angioedema attacks. The results of a second endometrial biopsy performed in October 2015 were normal. On November 24 she had swelling of one finger that lasted

for 5 hours. Progestin treatment was considered at that time, but because the patient did not experience additional angioedema episodes it was not introduced. The results of a third endometrial biopsy performed in October 2016 were again normal, and she had no further angioedema episodes as of her last visit in January 2017.

Most patients with normal C1INH-HAE worsen with estrogens.^{1,3} A subset of patients present with only angioedema after estrogen exposure, although the frequency of this estrogen-dependent phenotype varies among different patient populations (13% in a French series, 75% in a Spanish cohort, and 57% in a German series).^{1,7–9} Previously, the patient had angioedema attacks only during pregnancy. Thus, she was considered to have an estrogen-dependent phenotype. Estrogens influence the kallikrein-kinin system by increasing the FXII level and function and decreasing C1-INH levels, resulting in enhanced bradykinin production. High estrogen levels may also reduce bradykinin degradation through inhibition of angiotensin-converting enzyme expression while also inducing bradykinin type 2 receptor expression.^{1,3}

Endometrial hyperplasia represents a spectrum of morphologic endometrial alterations characterized by an increase in the endometrial gland-to-stroma ratio when compared with normal proliferative endometrium. It has been associated with the risk of progression to endometrial cancer of some atypical forms. Reversion to normal endometrium is the goal to prevent the development of adenocarcinoma.⁹ Endometrial hyperplasia usually occurs after menopause or during perimenopause, when ovulation ceases or becomes irregular and therefore progesterone declines or is no longer produced. As a result, the endometrium continues to grow in response to estrogen. This situation represents an imbalance between endogenous estrogen and progesterone with a relative excess of estrogen, which could explain angioedema attacks in this patient.

Cyclic progestin constitutes the major treatment option for EH without atypia by replacing endogenous progestin deficiency and producing a normal balance between estrogen and progesterone.⁹ Progestin has also proven benefits in the treatment of non-histaminergic angioedema, including patients with C1-INH HAE, normal C1-INH HAE, and idiopathic nonhistaminergic angioedema, decreasing the frequency of angioedema attacks while providing effective contraception.^{8,10}

In conclusion, we propose EH as a hyperestrogenic state causing angioedema attacks in a patient with estrogen-dependent FXII-HAE. Treatment with progestin avoided angioedema attacks while EH was also reversed. This case report supports progestin efficacy in nonhistaminergic angioedema.

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