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Case Report
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Extreme Hypersensitivity to Endogenous Progesterone

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Introduction

Progestogen Hypersensitivity (PH) is a rare disorder of unknown incidence and prevalence in which hypersensitivity-like symptoms are triggered by exposure to either endogenous progesterone or exogenous progestins [1]. Formerly known as Autoimmune Progesterone Dermatitis (APD), the condition has been increasingly referred to as PH due to a body of evidence suggesting its pathogenesis is most likely an IgE-mediated reaction and not due to the production of autoantibodies [2]. We present a case of this rare disorder that was found in an African-American female of child-bearing age and without exogenous Progestogen use.

Case Presentation

A 41-year-old African-American female patient presented to the Allergy Clinic complaining of swelling of her lips, tongue and face for the past few years. Other symptoms included difficulty swallowing, and changes in her voice. The patient denied shortness of breath, rash, visual changes, sneezing, rhinorrhea, cough, or wheezing. At the time of initial office visit the patient had no known allergies. She reported that these symptoms have been recurring every month a few days after her menstruation period, coinciding with the ovulation window. Skin testing was performed revealing positive results against progesterone. Having never been on any medication containing progesterone, it was concluded that her allergy was to endogenous progesterone. The patient was initiated on prednisone 20 mg orally every month for symptomatic control and was also given two epinephrine auto-injectors in case of emergency. Allergy shot immunotherapy was initiated to immunize to progesterone, however the patient did not respond appropriately. After a long course over 9 years to conservatively treat her rare allergy, she was ultimately referred to Gynecology for planned oophorectomy.

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Discussion

PH may present clinically with a heterogeneous range of dermatological and systemic symptoms including, but not limited to, urticaria, angioedema, pruritic clustered vesicular rashes, anaphylaxis, wheezing, and chest tightness in response to exposure to progestogens [3]. While the underlying derangements in physiology required to develop PH have not been elucidated, a prominent theory proposes that exposure to exogenous progestogens (oral contraceptive pills, *In-Vitro* Fertilization (IVF) treatments) causes the development of progestogen-specific IgE antibodies that cross-link to mast cells which subsequently degranulate in a type I hypersensitivity reaction [1]. However; this theory does not account for the reported cases in which the patient had no know previous exposure to exogenous estrogens [4].

Diagnosis of PH involves a careful history that temporally associates symptoms with exogenous progestogen administration or the progesterone surge of luteal phase of the menstrual cycle. This can then be followed by skin prick, progesterone challenge, or serological testing to confirm the diagnosis [3].

Multiple therapeutic approaches to PH have been reported with variable success. Importantly, therapeutic choices should be guided by the goals of the patient, specifically with respect to pregnancy desires and side effect tolerability. Generally, treatment is aimed at relief of hypersensitivity symptoms, ovulation suppression, or desensitization to the offending progestogen. Regarding symptomatic relief, oral H1 antihistamines and oral corticosteroids have demonstrated incomplete efficacy [1], while corticosteroids have well-documented and compliance-limiting side effects [5]. In a recent case, omalizumab, a monoclonal antibody directed at the IgE surface receptor on mast cells and basophils, was used successfully to treat PH [6]. In future practice, use of biologics like omalizumab may be limited by high costs [7]; however, they offer a promising potential treatment option for PH.

If a trial of symptomatic relief therapy fails, ovulation suppressants have been used as a next line of treatment. These medications have their own potential drawbacks. Unsurprisingly, combination Oral Contraceptive Pills (OCP's) are poorly tolerated due to the chance of a hypersensitivity reaction to low-dose progesterone within the OCP [1]. GnRH agonists and selective estrogen receptor modulators have been used to control symptoms with incomplete success and undesirable side-effect profiles that result from estrogen withdrawal [8,9]. For patients with severe symptoms who do not respond to the above therapies or desire pregnancy, cases of desensitization to progestogens with intramuscular, oral, and intravaginal progesterone have been reported to be successful [10,11].

Ultimately, in patients with severe and refractory symptoms to the aforementioned therapeutics, oophorectomy is a viable option for patients who are past child-bearing years or do not desire pregnancy that was first described by Shelley et al. in 1964 [12]. However, oophorectomy is a procedure with well-documented risks including decreases in cognition and sexual function along with increases in cardiac risk and osteoporosis [13-16] and should be used as a last resort.

Conclusion

PH is a very rare disorder that has little to no known incidence and prevalence in the U.S population. There are fewer than 200 reported cases worldwide. We present a rare case of PH that was refractory to standard therapies such as H1-antagonist, corticosteroids, and even Allergy shot immunotherapy. This patient was passed her child-bearing years, making her an appropriate candidate for surgical intervention. She is currently being managed by Gynecology with a plan to eliminate her PH *via* oophorectomy.

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