

CASE REPORT

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Progesterone Skin Test in Severe Attacks of Angioedema during Menstrual Cycle

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ABSTRACT

Progesterone hypersensitivity (PH) is a rare clinical condition that displays hypersensitivity to endogenous or exogenous progesterone. It is characterized by cyclic dermatologic manifestations at the end of the luteal phase that disappear some days after menses. We present a case of 24-year-old woman showing severe angioedema attacks occurring from the first day of her menstruation and continuing for 4-5 days and having positive progesterone intradermal test (IDT). To our knowledge, there is no case in the literature which is coupled with PH isolated angioedema attacks. In this case report we will discuss diagnostic value of progesterone IDT.

Keywords: Angioedema; Intradermal test; Premenstrual syndrome; Progesterone hypersensitivity

INTRODUCTION

Premenstrual syndrome (PMS) is characterized with a range of physical, psychological and behavioral symptoms that are not caused by any organic disease. Wide varieties of symptoms which may indicate this disorder include depression, mood lability, abdominal pain, breast tenderness, headache and fatigue.¹

Exact etiopathogenesis of PMS remains unknown, but several theories have been presented implicating

several hormones and neurotransmitters.²

Progesterone hypersensitivity (PH), also known as autoimmune progesterone dermatitis, is a clinical condition which is not very common and patients with this condition display hypersensitivity to endogenous or exogenous progesterone.³ Clinical symptoms include urticaria, eczematous eruptions, vesicles, pustules, erythema multiforme, and anaphylaxis.⁴ Both clinical conditions occur during the luteal phase of the menstrual cycle when the progesterone levels are high, and resolve partially or completely before or a few days after menses.^{1,3}

In this case report, a 24 year-old woman presented with severe recurrent attacks of angioedema occurring from the first day of her menstruation and continuing for

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4-5 days. We also aimed to evaluate the diagnostic value of progesterone intradermal test (IDT) with 50 mg/ml concentration which has been usually used in previously published case reports.

CASE REPORT

A 24 year-old female patient was referred to our clinic with angioedema complaint in her eyelids starting on the first day of her menstruation and continuing for 4-5 days for the last 6 months. The patient expressed that regular antihistamine medication before the menstruation neither prevented angioedema attacks nor shortened their duration. Angioedema was not associated with urticaria, dyspnea, eczema and anaphylaxis symptoms and significant complaints were related with PMS (depression, mood lability, abdominal pain, breast tenderness, headache and fatigue). The patient had an allergic rhinitis and asthma history for many years which deteriorated especially between March-July. Allergy skin test revealed the sensitivity to house dust mites and grass-cereals pollen mixtures. Allergen immunotherapy was started two years ago as medical treatment was not sufficient. The patient expressed that she benefited significantly from immunotherapy, although she sometimes took antihistaminic drugs due to rhinitis complaints for short periods of time. She did not have asthmatic complaints except for heavy physical exercise. She described no history of food and drug allergy. The patient also expressed that she took oral contraceptive drugs for a period of 2 months due to ovary cyst one year ago and that she ceased medication upon doctor's decision.

Except for the angioedema in her bilateral eyelids (Figure 1), the physical examination did not reveal any significant abnormalities. Laboratory evaluation included complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, anti-nuclear



Figure 1. Angioedema in bilateral eyelids

antibody, rheumatoid factor, liver tests, hepatitis B and C and HIV serologic tests, thyroid hormones, thyroid stimulating hormone, anti-thyroid peroxidase, C3, and C4 which were within normal ranges.

The progesterone skin test (Progestan ampoule ® 50 mg/ml; Koçak Pharmacy, Turkey) revealed no sensitivity. IDT performed with the same concentration was assessed 15 minutes later and 11x10 mm wheal was observed (negative control with saline was negative and histamine control showed a 13x18 mm wheal). With the diagnosis of PH, our patient was prescribed combination oral contraceptive containing 100 micrograms levonorgestrel and 20 micrograms ethinylestradiol (Miranova® Bayer, Turkey).

IDTs with 50 mg/ml progesterone were similarly performed in a control group consisting of 4 healthy and reproductive females who did not have PH or PMS history. In IDTs, wheal of 3 mm or more than that of negative controls was observed in all subjects of control group. When the tests were repeated with 5 mg/ml on 3 healthy women from control group, no reaction was observed. The fourth woman from control group did not accept to have the second test. Two months later, on the patient's control visit, she reported that she did not suffer from angioedema attack during the last two menstrual cycles when she used oral contraceptives. IDT with 5 mg/ml progesterone was performed for the patient after treatment and no reaction was observed.

DISCUSSION

As it is a very rare disorder, PH should be considered a diagnosis of exclusion. Menstrual cycle related skin lesions or allergic symptoms, positive response to allergy test with progesterone and symptomatic recovery after progesterone secretion inhibition by suppressing ovulation are strong indications to consider the existence of PH.⁵ In contrast to PH, PMS is a common disorder in women of reproductive age. At least one premenstrual symptom occurs in 95% of women of reproductive age.¹ Women with PMS experience a wide range of symptoms and such symptoms can quite vary in terms of severity. Some of these symptoms experienced by women may be so severe that it is emotionally and physically disabling.

Actually, severe recurrent angioedema only limited to her eyelids occurring from the first day of her menstruation and lasting for 4-5 days was not associated with symptoms of PMS and mainly indicated PH. To

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our knowledge, there is no case of PH characterized by isolated angioedema attacks in the literature.

Although our patient's angioedema attacks did not coincide exactly with the one week before menstrual period when the progesterone reaches peak level, the fact that the complaints were of cyclical nature, and did not respond to antihistaminic drugs and that the IDT with progesterone (50 mg/ml) was positive made us think of PH. For this reason, our patient was prescribed oral contraceptive medication containing conjugated estrogen to suppress the ovulation and she was called for follow up 2 months later.

Depending on their concentration, the IDT with the drugs may give high rates of false positive results and there is no study carried out to determine the non-irritant concentration of IDT with progesterone for PH which is a rare clinical case. For these reasons, a control group of 4 healthy and reproductive females underwent IDT with 50 mg/ml progesterone. The fact that the IDT of 50 mg/ml concentration at all individuals in our control group resulted positive in terms of early reactions made us think that 50 mg/ml concentration used in IDT with progesterone for PH diagnosis may lead to false positive results.^{3,6,7}

Even though we thought that IDT did not have sufficient diagnostic value in our patients, the angioedema attacks terminated in the 2 month cycles during which the ovulation was suppressed and this supported our diagnosis of the PH. Our patient used drugs containing exogenous progesterone for a short period of time in the past and a previous exposure to a synthetic progestin might have stimulated the immune system to produce antibodies that cross-reacted with endogenous progesterone.⁵ The fact that our patient also had allergic rhinitis and asthma may be considered as a finding in favor of PH diagnosis as seen in many cases in the literature.^{3,7,8}

It is known that intra-muscular challenge test with progesterone was considered to be valuable in the

diagnosis of the case, the test was not performed due to its potential risk taking the characteristics of the allergic reaction into consideration. In conclusion, it must be taken into consideration that in diagnosis and treatment of PH, IDT tests with progesterone may give high rates of false positive results; and clinical picture and response to the treatment must be assessed primarily.

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