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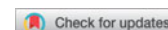
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Perimenstrual asthma: Report of a case with therapeutic intervention of oral prednisone

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ABSTRACT

Introduction: Many asthmatic women of childbearing age experience cyclical aggravation of asthmatic symptoms during the perimenstrual period, or perimenstrual asthma (PMA). PMA is considered to be a difficult-to-treat asthma phenotype; conventional asthma therapies are not always effective against PMA. **Case Study:** We report a case of a 27-year-old female with PMA who had received standard asthma treatment since 2013. **Result:** The patient showed a dramatic response to therapeutic intervention of oral prednisone, taken for 7 days prior to menstruation each month, in a dose-dependent manner. **Conclusion:** Premenstrual treatment with oral prednisone may be a successful new direction for the treatment of PMA, a troublesome type of asthma.

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Introduction

Asthma is one of the most common chronic airway inflammatory diseases, affecting approximately 300 million people throughout the world. It is characterized by airway constriction that contributes to episodes of wheezing, coughing, chest tightness, and shortness of breath (1). Nowadays, it is estimated that up to 40% of asthmatic women of childbearing age may experience cyclical aggravation of asthmatic symptoms during the perimenstrual period. This phenomenon is referred to as perimenstrual asthma (PMA) (2,3) and is considered to be a difficult-to-treat asthma phenotype. Even though the associations between sex hormone (progesterone and estradiol) levels and airway hyperresponsiveness and between the menstrual cycle and airway hyperresponsiveness have been assessed (4), no specific relationship between these factors has been confirmed. Adrenocorticosteroid agents or hormone therapy have been used to treat PMA (5), but no internationally accepted therapeutic guidelines have been established to handle this troublesome type of asthma.

Here we present a case of PMA followed for 4 years in our outpatient pulmonary clinic in which the

administration of prednisone premenstrually was an effective therapeutic intervention.

Case study

A 23-year-old woman was admitted to our outpatient department on October 3, 2013 because of sudden onset of cough and tachypnea. She had a normal menstrual cycle and volume, and had no gynecological surgery or injury or relevant family history. No abnormal findings were revealed upon physical examination except the distribution of scattered wheeze during the expiratory phase of breathing. Pulmonary function tests showed severe obstruction of ventilation function (FEV_1 %pre: 43.3%; FEV_1 /FVC%: 48.95%) and positive bronchodilation test. Genetic testing indicated the presence of at least 5 alleles associated with susceptibility to asthma: *IL13* c.431A>G, *ADRB2* c.46G>A, *ADRB2* c.79G>C, *PLA2G7* c.1136T>C, *NPSR1* c.320A>T. All of the above findings supported the diagnosis of asthma. Therefore, we prescribed long-term regular inhaled corticosteroids (ICS, dry powder 50 µg/250 µg Seretide q12h) and oral medications (10 mg Montelukast Sodium Tablets qn, 0.2 g

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Docofylline bid, and 0.3 g Eucalyptol tid), and suggested that she continue to have follow-up examinations in our outpatient department every 2 months.

During the follow-ups of past 4 years, as we observed the patient's respiratory symptoms and fractional exhaled nitric oxide (FeNO, normally less than 25 ppb) results in conjunction with her menstrual cycle (Figure 1), we noted a potential relationship between her asthma aggravation and menstrual cycle. Beginning with the observation on July 3, 2014 that her asthma exacerbation was on the second day of her period, we repeatedly observed that her asthma attacks occurred 2–3 days before the onset of menstruation and lasted for around one week. In February, 2015 we added oral prednisone (30 mg qd $\times$ 7d) for one week before menstruation to the patient's therapy regimen, in conjunction with conventional therapies. In response, her asthma symptoms and airway inflammation were substantially ameliorated for more than 18 months. A pulmonary function test on August 4, 2016 showed improvement compared to the initial findings on October 3, 2013 (FEV₁%pre 50.5%; FEV₁/FVC%: 52.76% vs. FEV₁%pre: 43.3%; FEV₁/FVC%: 48.95% and negative bronchodilation test).

In the month of February, 2017, she reduced the dosage of oral prednisone by half (15 mg qd $\times$ 7d) without approval, leading to a rebound of asthma symptoms and a higher level of FeNO (182 ppb), as measured on March 1, 2017. In response we began to gradually increase the dosage of oral prednisone, starting with 20 mg qd $\times$ 7d, to relieve her worsened respiratory symptoms. On April 27, 2017, 3 days prior to her menstrual cycle, her level of FeNO had decreased to 107 ppb, demonstrating a dose effect of oral prednisone. On April 27, 2017 we

also measured serum levels of sex hormones, which were found to be in the normal range.

Discussion

PMA, a hard-to-treat and even life-threatening asthma phenotype, describes that some female asthmatic patients experience the nadir of their symptom control just during the premenstrual or menstrual period. More recent studies have focused on the cause and therapy of PMA. Even though female sex hormones play an important role in the cause of PMA seems intuitively obvious, the cyclical asthmatic aggravation of women with PMA may be owing to the recently identified oestradiol-receptor-dependent mast-cell activation, the specific mechanisms through which the hormones affect asthma symptoms, however, remain obscure (6,7).

There are no specific guidelines for PMA treatments. The management of PMA, including medical interviews, can play a vital role in actual clinical settings. Currently, the large majority of women with PMA receive the same treatment as other asthma patients, namely long-term regular inhaled corticosteroids and β_2 agonists combined with oral leukotriene receptor antagonists, expectorants and so forth; in several (but not all) researches of PMA, the inhaled glucocorticosteroids, intramuscular progesterone, oral contraceptive pills (OCPs) (8), or leukotriene receptor antagonists (LTRA) (9) allow good symptom control during the perimenstrual period. However not all women with PMA respond effectively to these conventional asthma therapies (10), such as in the case presented here. In this case, we found that a therapeutic intervention of oral prednisone (30 mg qd $\times$ 7 d) for a week

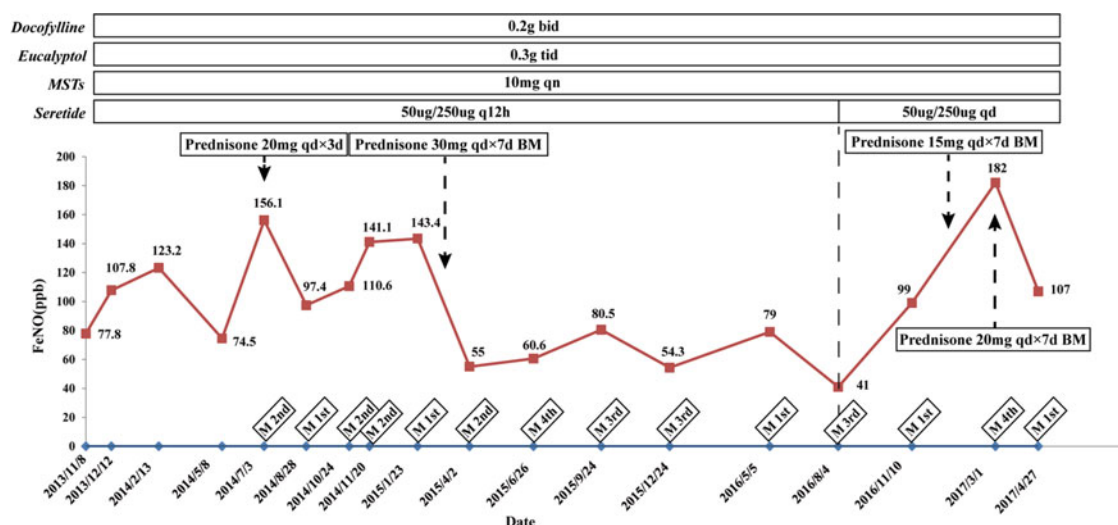


Figure 1. Effect of oral prednisone on fractional exhaled nitric oxide. Fractional exhaled nitric oxide (FeNO) readings are shown with respect to treatment and patient's menstrual cycle. M 1st: first day of menses; M 2nd: second day of menses; M 3rd: third day of menses; M 4th: fourth day of menses; MSTs: Montelukast Sodium Tablets; BM: before menses.

before menstruation in conjunction with conventional therapies can attenuate the asthma aggravation during the menstrual cycle. The mechanism of prednisone action probably involves regulation of sex hormone secretion and airway inflammation but further investigation is needed before conclusions about mechanisms can be reached. Our current report is limited by the lack of data on sex hormone levels during the period of asthma aggravation, and before and after the therapeutic intervention of oral prednisone.

Conclusion

Effective treatment for PMA is lacking, but this case report suggests that non-conventional therapies like premenstrual oral prednisone have the potential to attenuate PMA symptoms. More scientific research and clinical trials will be required to identify the optimal treatment regimens for PMA patients.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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