Case Report

Recurrence of Symptoms Associated with Menstruation in a Patient with a History of Periodic Fevers

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A B S T R A C T

Background: Periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome is a cyclic autoinflammatory disease generally diagnosed in childhood. There have been studies suggesting a relationship between menstruation and other autoinflammatory syndromes such as familial Mediterranean fever (FMF), but not PFAPA specifically.
Case: This case describes a patient with a diagnosis of PFAPA who experienced complete resolution with tonsillectomy only to have recurrence of symptoms with onset of menstruation. She experienced symptom control with initiation of oral contraceptives.
Summary and Conclusion: Prior to this case report, there had been no evidence in the literature suggesting a relationship between PFAPA and menstruation despite the observed association in other autoinflammatory syndromes. Onset of menses may be a trigger in PFAPA.
Key Words: Periodic fever, Aphthous stomatitis, Pharyngitis, Adenitis, PFAPA, Familial Mediterranean fever, Menstruation, Catamenial, Inflammation, Fever, Menstruation-induced

Introduction

A number of studies in the literature have suggested an association between periodic fevers and menstruation. It has been reported that up to 15% of women with familial Mediterranean fever (FMF) have experienced a flare during menstruation,[1] with a more recent study suggesting 33%.[2] Several more recent case reports have noted the same association.[3,4] Other studies have attempted to explain this association, and have suggested that hormone changes such as decreases in estrogen levels during menstruation induce inflammatory pathways and potentially lead to symptoms.[5,6] The majority of the limited literature available centers on FMF. There is scarce information available regarding the association between menstruation and other periodic fever syndrome flares. In this case report, we present a patient with a history of periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome (PFAPA) that experienced resolution with standard treatment who then had subsequent recurrence of symptoms with menarche. Currently, a diagnosis of PFAPA is made when the constellation of clinical symptoms previously mentioned is present. There are no universally accepted diagnostic criteria.

Case

The patient initially presented to rheumatology in 2014 as a 10-year-old with complaints of joint pain and recurrent episodes of high fevers, sore throat, and fatigue. She had experienced 3 episodes that were each 5 weeks apart, prior to presentation to rheumatology, with a temperature maximum recorded as 104°F at home. Each episode of fever was accompanied by sore throat and lymphadenopathy. Joint pains were primarily in the knees and did not fluctuate with episodes of fever. Symptoms occurred 2 to 3 days out of the week, most often in the evenings and throughout the night. In regard to her joint pain, it responded to ibuprofen and heat therapies. She also underwent physical therapy, which reportedly was helpful. Her knee pain was ultimately determined to be secondary to bilateral knee injuries sustained in 2013 for which she eventually required surgeries in 2015 and 2017 for recurrent bilateral patellar instability. Knee pain resolved after this time and did not recur. Her other symptoms were ultimately attributed to PFAPA, and she was referred to otorhinolaryngology for an adenoidectomy and tonsillectomy, which was completed in 2014. After her surgery, there was complete resolution of her symptoms.

Past medical history consisted of benign extra-axial fluid collections of infancy and 1 episode of bronchiolitis. Her family history included hypertension and hypercholesterolemia in her father, Hashimoto thyroiditis in her mother, and no medical problems in her sister.

The patient's first menstrual period occurred in December 2015. She started to notice symptoms including fevers, headaches, malaise, sore throat, and swollen lymph nodes that seemed to occur in conjunction with her menses. Fevers would be the initial symptom and start about 1 day before menstruation. Symptoms would last between 3 and

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4 days and then completely resolve. She did visit her pediatrician at this time and was given a short course of prednisone, which improved her symptoms. Her pediatrician decided to place her on a combined hormonal oral contraceptive. She was initially started on desogestrel–ethinyl estradiol 0.15-0.03 mg. She continued on this for about 1 month but developed worsening anxiety and had to stop use. She was subsequently started on norethindrone acetate–ethinyl estradiol 1-0.01 mg. She was able to tolerate this from August 2018 through October 2018, during which time she experienced complete resolution of symptoms. However, she eventually stopped use of this pill as well, because of worsening anxiety. Symptoms recurred once the birth control pill was discontinued. She did seek re-evaluation by rheumatology in December 2018, and further workup was completed.

Bloodwork at that time included TSH 1.05 MIU/L, free T4 2.73, T4 total 9.6 μg/dL; thyroglobulin antibodies and thyroid peroxidase antibodies were negative, rheumatoid factor IgG was elevated at 12 U (normal <6 U), and rheumatoid factor IgM was elevated at 30 U (normal <6 U). An antinuclear antibody (ANA) screen was negative, and cyclic citrullinated peptide IgG was negative as well. Inflammatory markers were not obtained. Her total testosterone was 17 ng/dL, free testosterone 1.8 pg/mL, progesterone 1.8 ng/mL, prolactin 11.4 ng/mL, follicle-stimulating hormone (FSH) 4.3 mIU/mL, luteinizing hormone (LH) 5.3 mIU/mL, DHEAS 189 μg/dL, and estradiol 76 pg/mL. A complete metabolic panel was entirely within normal limits. A complete blood count was essential unremarkable aside from a slightly low mean corpuscular volume (MCV) of 76.8 FL (78.0-98.0) and slightly high red cell distribution width (RDW) of 16.5% (11.0-15.0). White blood cell count and differential were within normal limits. Platelets were slightly elevated at 545,000/μL. Of note, Epstein-Barr virus (EBV) titers had been sent for evaluation during a previous symptomatic event in May of 2018, which were negative. In regard to imaging studies, a thyroid ultrasound was performed, which was unremarkable and without evidence of nodules or enlargement.

Rheumatology ultimately deemed that her symptoms were not likely due to a monogenic periodic fever syndrome, and no further workup including genetic testing was completed. This decision was reached because of the lack of symptoms consistent with FMF, specifically absence of abdominal pain, joint pain, and rash as well as her lack of a positive family history. They also concluded that her constellation of symptoms fit the pattern of PFAPA. Her elevated rheumatoid factor was deemed a false-positive result.

She was then referred to adolescent medicine for further evaluation and symptom management. Her initial appointment was in March of 2019. The patient was determined to be healthy in appearance, with a body mass index of 29.65 kg/m^2. Previous evaluations and workup were reviewed. She was not on any medications. She denied any tobacco use, alcohol use or illicit substances. She denied any history of sexual activity and was currently attending high school. The blood work mentioned above had been obtained approximately 4 months prior to her initial visit in our clinic. Her menstrual history was reviewed. Since December 2018, the patient had experienced 3 regular menstrual cycles with identical preceding symptoms including headache, sore throat, lymphadenopathy, and fever. She did mention that during her menstrual cycle in January 2019 she had been diagnosed with bacterial sinusitis and was treated with antibiotics, so it could not be validated that her symptoms were secondary to her menstrual cycle alone during that particular time. Despite this, we did observe that her symptoms appeared to coincide with her menstrual cycle. Given her previous issues with worsening anxiety on estrogen-containing hormonal contraception, we opted to start the patient on a progesterone-only method. The patient did not wish to start medroxyprogesterone depot and so was started on norethindrone 0.35 mg daily.

She has been seen in follow-up twice since starting this medication. She has maintained excellent compliance. At her 5-month follow-up, she had experienced 1 episode of premenstrual symptoms, but considered that they were much more mild in severity and lasted for only 1 day. All other months she remained symptom free. She described her periods as regular without any breakthrough bleeding. She denied any symptoms of dysmenorrhea or heavy menstrual bleeding.

Summary and Conclusion

PFAPA is a syndrome, first described in 1987, manifesting as fever, aphthous stomatitis, pharyngitis, and adenitis. It is cyclic in nature, with symptomatic episodes occurring about every 4-6 weeks and lasting 4-5 days. Symptoms spontaneously resolve, and most patients are without symptoms between episodes. Treatment has included acetaminophen, nonsteroidal anti-inflammatory drugs, steroids, and tonsillectomy with or without adenoidectomy. Steroid use and surgical intervention have had the most consistent results, with either notable reduction in symptom severity or complete resolution of symptoms.[7]

The pathogenesis of PFAPA is unclear. There is suggestion of a genetic component; however, studies have not revealed consistent results and have not found variants in a particular gene. Most patients with a diagnosis of PFAPA lack the mutations that have been implicated in other periodic fever syndromes such as FMF.[8] Of those patients who were identified to have genetic variants in genes associated with other autoinflammatory syndromes, studies have looked at whether patients with PFAPA had higher than expected prevalence of variants; however, results have been conflicting.[9]

The ready response to prednisone in many cases suggests that dysregulation of cytokines is involved in the episodes of PFAPA. There have been studies that have found elevations in several cytokines including interferon-γ, tumor necrosis factor–α, and interleukin-1, -6, and -18, suggesting activation of the innate immune system.[10,11] Elevated levels of interleukin 1 are also seen in other autoinflammatory syndromes such as FMF, which suggests similarities in their pathogenesis.[12]

There are other similarities between PFAPA and FMF, and many patients with an ultimate diagnosis of PFAPA are initially suspected to have FMF. In addition to the usual features of PFAPA, patients sometimes also exhibit mild to moderate joint and abdominal pain, as can be seen in FMF. However, FMF-associated joint pain is usually more severe, as is the experienced abdominal pain. Both syndromes are associated with fever; however, PFAPA is cyclic as compared to flares of FMF, which tend to be unpredictable.[13]

There is limited information regarding potential triggers of PFAPA, as it is cyclic in nature with a highly predictable pattern. This pattern is generally maintained regardless of the presence or absence of triggers identified as causing flares in other periodic fever syndromes. There is virtually no literature on a possible association between PFAPA flares and menstruation. However, there have been case reports suggesting a relationship between menstruation and flares of FMF.[3,4] Given some of the similarities in presentation as well as pathogenesis, menstruation could potentially lead to flare or symptom recurrence in patients with a history of PFAPA, as is suggested in this case.

There is some literature looking into the relationship between FMF flares and menstruation. Studies finding an association have been consistent; however, percentages of patients affected have varied. A study published in 2013 found that one-third of 275 patients experienced a perimenstrual attack.[2] Other studies have attempted to investigate the pathogenesis of such an association.

The current hypothesis centers around estrogen as a protective mechanism against attacks. As estrogen levels decrease during the menstrual cycle, the protective effect is lost, allowing for a potential flare. This hypothesis was developed based on the observation that initiation of oral contraceptives has helped in flare, which is primarily demonstrated in case reports1.[14] Hormone replacement therapy has also been shown to lower the expression of intercellular adhesion molecules, which are thought to precipitate attacks.[5] In addition, there is evidence that estrogen can inhibit tubulin assembly, leading to prevention of attacks.[15] Given the similarities in pathogenesis between PFAPA and FMF, the protective effects of estrogen may be attributable to PFAPA as well and may help, in part, to explain why our patient began to experience flares with onset of menstruation.

The argument for estrogen may be further supported by the observation that PFAPA tends to present in early childhood, with resolution of most cases by adolescence or adulthood. It is understood that prepubertal estradiol and estrone levels are lower than pubertal levels.[16] This suggests that puberty should provide additional protection from flares as estrogen levels are increased; however, our patient experienced recurrence of symptoms with menarche.

Furthermore, our patient's symptoms also responded to a progesterone-only method of birth control. Progestin-based methods are known to decrease levels of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), eventually leading to a reduction in estradiol levels and anovulation.[17] Despite this, our patient experienced improvement in symptoms, suggesting that the relationship between PFAPA and the menstrual cycle is much more complex and is likely mediated by several additional factors. Progesterone may provide its own protective effect, although this has not yet been studied specifically. It also may be that progestin-only methods of birth control provide more stable levels of estrogen even if decreased overall leading to avoidance of abrupt withdrawal, which is a potential trigger for flare.

In conclusion, PFAPA is a cyclic autoinflammatory syndrome not previously reported to be triggered by menses. However, a relationship has been described between menstruation and another autoinflammatory syndrome, FMF. Combined hormonal oral contraceptive pills have been used in the treatment of menstrually mediated flares in FMF with the suggestion that estrogen plays a protective role. Our patient was treated similarly with good response; however, she has also responded to a progesterone-only method. The role of progesterone in this case requires further investigation.

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