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CASE BASED REVIEW

Recurrence of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome after tonsillectomy: case-based review

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Abstract
Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a recurrent fever syndrome for which tonsillectomy is a therapeutic option curing the disease in most patients. Recurrence after remission with tonsillectomy is extremely rare. Increasing number of reports on diverse disease manifestations in PFAPA could give us clues about the disease etiopathogenesis. We aimed to describe a patient with recurrence of PFAPA syndrome after tonsillectomy and to review the previous studies including similar cases. We report a 17-year-old boy with PFAPA syndrome who experienced remission for 3 years after tonsillectomy and was later found to harbor an *MEFV* mutation when the disease relapsed. He responded well to colchicine treatment at relapse. The literature review revealed 14 articles describing 24 similar PFAPA patients. The therapeutic options include single-dose corticosteroids and nonsteroidal anti-inflammatory drugs during attacks, cimetidine, and resurgery. The presented case was the only one heterozygous for an *MEFV* mutation and treated with colchicine at disease relapse. Albeit rare, the reoccurrence of PFAPA after tonsillectomy could occur. The presence of such patients opposes with the hypothesis that the trigger or immune dysregulation in PFAPA pathogenesis resides in tonsils.

Keywords PFAPA syndrome · Tonsillectomy · Relapse · Recurrence

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome was first described in 1987 by Marshall et al. [1]. It is characterized by regularly occurring febrile attacks of pharyngitis, oral aphthous lesions, and enlarged cervical lymph nodes [2]. PFAPA syndrome mainly occurs in early childhood (before 5–6 years of age) [3, 4]. Its etiopathogenesis remains unknown. The results of the recent studies on pathogenesis suggest that the innate immune system is activated first, mediated by inflammasomes followed by a T-cell-mediated adaptive immune response [5–7]. However, the trigger of the inflammation has not been identified yet.

The management of PFAPA syndrome includes both medical and surgical therapeutic options. The most effective medical treatment for acute attacks is single-dose corticosteroids [8]. However, it could cause an increase in the attack frequency [9, 10]. For decreasing attack frequency, there are different therapies such as cimetidine, colchicine, and tonsillectomy along with new options such as interleukin 1 (IL-1) inhibitors [2, 11]. Tonsillectomy remains the most effective therapy with the highest rate of cure [12]. In the most recent systematic review, Førsvoll et al. [12] have shown that the disease was cured with tonsillectomy in 92% of cases. The level of evidence for tonsillectomy in PFAPA syndrome is 1a in the presence of two randomized controlled trials demonstrating its high efficacy for curing the disease [13, 14]. However, the disease is self-limited which makes it difficult to recommend surgery to every case. It is essential to make the decision as a team with the family and evaluate each case separately. Moreover, one should keep in mind that tonsillectomy may not cure the disease or the disease may reoccur later in the follow-up. In patients who do not achieve cure

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with tonsillectomy, it is critical to search for other causes of recurrent fever attacks such as cyclic neutropenia, recurrent upper respiratory tract infections, and monogenic autoinflammatory diseases such as familial Mediterranean fever (FMF) or hyperimmunoglobulin D syndrome/mevalonate kinase deficiency [2].

Disease relapse after tonsillectomy is extremely rare. This study aimed to report our experience with an adolescent boy who had PFAPA syndrome relapse after tonsillectomy and to investigate the characteristics of similar cases in the literature.

Search strategy

PubMed/MEDLINE and Scopus databases were screened according to the published guidance on narrative reviews [15] by entering the following keywords: "PFAPA syndrome", "periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis", "Marshall's syndrome", "tonsillectomy", and "adenotonsillectomy" from database inception to March 1, 2019. Randomized and nonrandomized controlled trials, observational studies (case–control, cohort studies, and case series), and single-case reports were investigated and all publications reporting PFAPA patients who had disease relapse after remission with tonsillectomy were included. The search was restricted to the English and German articles. Two authors (EDB and HBB) independently screened titles, abstracts, and full texts of all relevant articles. The following parameters were noted from included studies: gender, age at disease onset, age at diagnosis, age at tonsillectomy, age at relapse, disease duration before tonsillectomy, the symptoms during attacks, the duration of attacks and inter-attack periods, previous therapies other than tonsillectomy, recent treatment (of relapse), and response to treatment (after relapse).

Case report

A 17-year-old Turkish boy admitted to the hospital with complaints of recurrent fever attacks. He was having recurrent fever, pharyngitis, oral aphthosis, and cervical lymphadenitis attacks, since he was 4 years old. Throat swabs did not reveal any infectious origin, and there was no response to antibiotic treatment. The attacks were recurring every month and lasting for 3–4 days. Oral aphthosis was present in all attacks, while tonsillitis was present in most and cervical lymph nodes were enlarged in several attacks. Adenotonsillectomy was performed when he was 6 years old, and he had not had any attacks until he was 9 years old. The disease recurred when he was nine with the same type of attacks. There were no other symptoms such as abdominal pain, chest pain, arthralgia, and arthritis during attacks neither before nor after tonsillectomy. He had oral aphthosis sometimes in the attack-free periods, as well. He did not have any other symptoms suggesting Behçet's disease such as genital aphthosis, pseudofolliculitis, acneiform lesions, and history of vascular events or uveitis. Moreover, his pathergy test was negative. The C-reactive protein was 58 mg/L (normal range 0–5) during attack. In family history, his elder sister also had similar attacks when she was 4 years old. She was cured after tonsillectomy at the age of 6 years and the disease did not recur. She is currently 21 years old. There was recurrent oral aphthosis in his father and both grandmothers which suggests familial recurrent aphthous stomatitis. His grandmother (mother of his mother) had FMF.

The diagnosis of PFAPA was made in the presence of three core symptoms of disease (pharyngitis, aphthous stomatitis, and cervical adenitis) in most attacks. *MEFV* mutations were analyzed with next-generation sequencing, where all exons were sequenced. He was heterozygous for M694V. Colchicine treatment was initiated which significantly decreased the frequency of disease flares. He was having one attack per month before colchicine. He had only one attack in the follow-up period of 8 months after the initiation of colchicine.

Patients with recurrence of PFAPA after remission with tonsillectomy in the literature

The schematic overview of the studies included in this review is shown in Fig. 1. We identified 14 articles describing 24 PFAPA patients with reoccurrence of PFAPA syndrome after a period of remission with tonsillectomy during the literature search [10, 16–28]. The characteristics of 11 patients from these articles are summarized in Table 1 along with the presented case. Monogenic autoinflammatory diseases were excluded with either clinical features or genetic tests in most of these patients. In the rest of the reported patients ($n = 13$; five from the article by Vigo et al. [23], three from the article by Lantto et al. [27], three from the article by De Pieri et al. [28], and one each from the articles by Rigante et al. [10] and Pignataro et al. [22]), no further data were available except that they experienced recurrence of disease after an initial response to tonsillectomy.

The presented case is the only-PFAPA patient treated with colchicine for the relapse after remission with tonsillectomy.

Discussion

It is a rare situation for PFAPA patients to experience a recurrence of disease after remission with tonsillectomy. There are 25 such patients (including the presented case)

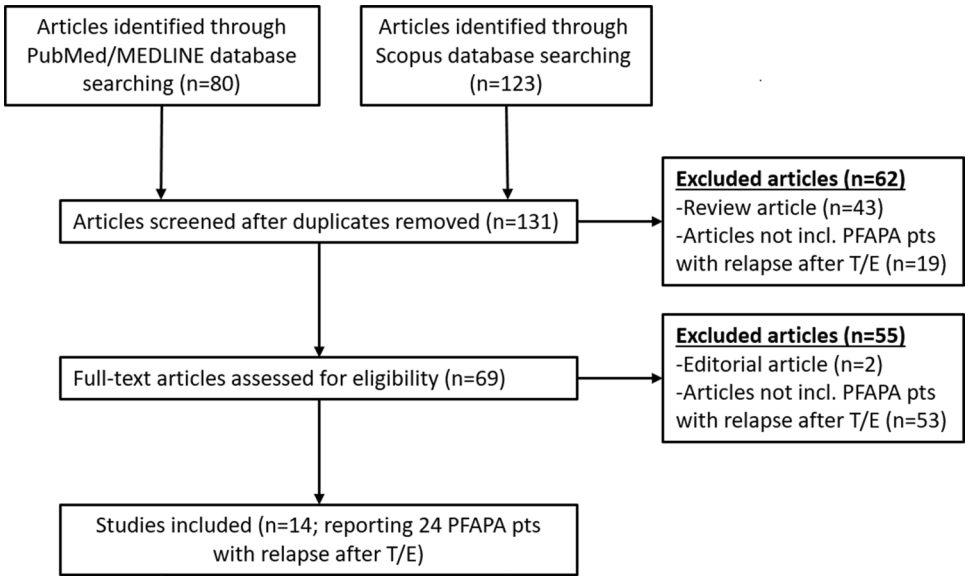

Fig. 1 Schematic overview of the studies on recurrence of PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome after tonsillectomy included in the literature research (*pts* patients, *T/E* tonsillectomy)

Table 1 Characteristics of PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) patients with reoccurrence of the disease after tonsillectomy in the literature

References	No. of pts.	Sex	Age at sx onset	Age at *T/E*	Duration of remission after *T/E*	Age at relapse	Exclusion of monogenic AIDs	Tx of relapse	Outcome (follow-up)
Ridder [19]	1	F	8 months	4 years	11 years	15 years	HIDS/MKD[a]	Cimetidine	No response (6–8 months)
Parikh [21]	1	M	~5 years	5 years 9 months	3 years	6 years	N/A	No tx	Ongoing episodes
Colotto [16]	1	F	1 year	4 years	11 years	15 years	Clin. excl.	Single-dose cs during attacks	No attacks after 21 yoa (till 26 yoa)
Onderka [18]	2	F	7 months/6 months	2.5 years/4 years	4 years/12 years	6.5 years/16 years	Clin. excl.	Single-dose cs during attacks	N/A
Cantarini [25]	1	M	24 years	N/A	A few months	27 years	FMF, HIDS/MKD, TRAPS, CAPS[a]	ANK	No attacks under ANK (6 months)
Krol [20]	2	N/A	<5 years	N/A	12 months/14 months	N/A	HIDS/MKD[a]	Antipyretics and cs during attacks	Attack-free for 5–6 months (10 months/21 months)
Forsvoll [26]	1	F	1 year	40 months	6 months	46 months	HIDS/MKD, TRAPS, CAPS[a]	N/A	Less frequent and shorter attacks than pre-op
Lantto [17]	1	F	N/A	N/A	Several years	N/A	Genetic excl.	Repeat surgery	N/A
Vitale [24]	1	N/A	Infancy	N/A	Long term	14 years	N/A	N/A	N/A
Present case	1	M	4 years	6 years	3 years	9 years	M694V/–	Colchicine	Less frequent attacks (8 months)

Ab antibiotic, *AID* autoinflammatory disease, *ANK* anakinra, *clin. excl.* clinical exclusion, *F* female, *HIDS/MKD* hyperimmunoglobulin D syndrome/mevalonate kinase deficiency, *M* male, *N/A* not available, *T/E* tonsillectomy, *tx* treatment, *yoa* years of age

[a]Excluded with genetic tests

reported to date. The presented case is the only one heterozygous for an *MEFV* mutation and treated with colchicine during relapse.

Some authors hypothesized that either the immune dysregulation itself or the trigger resides in tonsils in PFAPA syndrome, since the inflammation is usually restricted to

the oropharyngeal tissues and there is a high rate of cure with tonsillectomy [29, 30]. Recurrence after remission with tonsillectomy or lack of response to tonsillectomy suggests that the hypothesis above may not be true at least for some patients who continue experiencing attacks after removal of tonsils.

In the reported cases with recurrence of disease after remission with tonsillectomy, the age of tonsillectomy was around 4–6 years of age [16, 18, 19, 21, 26]. There seems no association between the age at tonsillectomy and duration of remission after tonsillectomy (Table 1). The relapse of PFAPA occurred in childhood/adolescence in most [16, 18, 19, 21, 24, 26] except one patient who experienced relapse at 27 years of age [25]. However, the disease onset was also in adulthood in this patient.

The disease remained silent for a period after tonsillectomy in the presented patient and 24 patients reported in the literature. The reasons for this temporary remission and the reoccurrence of disease afterward are unknown. We could not identify a possible trigger of disease flares such as a major change in environmental exposure or stressful events. One possible explanation could be tertiary lymphoid organogenesis causing disease relapse.

For most of the reported cases with relapse after tonsillectomy, monogenic autoinflammatory diseases had been excluded with genetic tests or clinical measures. Since this disease course is atypical for PFAPA, differential from monogenic autoinflammatory diseases is essential. *MEFV* was the first gene to test among genes of autoinflammatory diseases, since our patient was from an FMF-endemic area. He was heterozygous for M694V on *MEFV* gene. *MEFV*, the gene associated with FMF, encodes for pyrin protein and mutated pyrin causes uncontrolled IL-1β secretion leading to an exaggerated inflammatory response [31, 32]. This increase in IL-1β secretion may also contribute to the PFAPA pathogenesis. Previous studies suggest that carriers of *MEFV* variants have a more "pro-inflammatory" phenotype than wild-type (WT) controls. For instance, several inflammatory diseases such as immunoglobulin A vasculitis/Henoch–Schönlein purpura, rheumatoid arthritis, and acute rheumatic fever were more frequent and greater basal and peak concentrations of acute phase reactants have been observed among *MEFV* variant carriers compared to WT controls [33–37]. Moreover, Federici et al. proposed that a "dose effect" was present associated with *MEFV* mutations as increasing PFAPA-like symptoms and decreasing FMF-like symptoms from patients carrying one low penetrance *MEFV* mutation towards those homozygous for two high penetrance *MEFV* mutations [38].

The frequency of *MEFV* variants among PFAPA patients ranges from 8 to 66% [2]. These variants may affect PFAPA phenotype [39–45]. No difference was detected between PFAPA patients with and without *MEFV* variants in several studies [33, 46–48], while some have shown a modifier effect of *MEFV* variants on disease phenotype [39, 44, 45]. This effect seems favorable with shorter duration of attacks, longer attack-free intervals, and response to lower doses of corticosteroids during attacks [39, 44, 45]. Besides, the response rate to colchicine was higher, symptoms such as abdominal pain, myalgia, and arthralgia, and family history of recurrent fever were more frequent among PFAPA patients with *MEFV* variants compared to those without variants [40–43]. About response to tonsillectomy, Pehlivan et al. reported that the response rate was lower in PFAPA patients with coexistence of FMF features compared to those without FMF-like features [43]. There is no report about the effect of *MEFV* variants on self-limited disease course or disease relapse after remission with tonsillectomy. The main reason for this could be the deficiency of studies with very long follow-up periods which could demonstrate both the self-limited course and relapse after remission. *MEFV* variants may increase the risk of relapse after remission. However, this should be tested in large PFAPA cohorts with a long period of follow-up after remission.

Several drugs such as cimetidine, colchicine, IL-1 inhibitors, vitamin D, pidotimod, and probiotic K12 have been used to decrease the frequency of attacks in PFAPA syndrome [2, 49]. Colchicine, the mainstay of FMF treatment, causes release of a RhoA activator by depolymerizing microtubules [50, 51]. Effector kinases of RHoA suppress pyrin inflammasome leading to decreased production of IL-1β [51]. Park et al. demonstrated that colchicine inhibits IL-1β release from mononuclear cells of FMF patients [51]. Previous studies have demonstrated that stimulated peripheral mononuclear cells of PFAPA patients produce high levels of IL-1β and serum IL-1β levels increase during PFAPA flares [5, 52]. Colchicine may be beneficial in PFAPA treatment by decreasing IL-1β production. There is only one randomized controlled trial on use of colchicine in PFAPA [47]. In their study, the number of PFAPA attacks significantly decreased among patients receiving colchicine treatment, whereas the attack frequency did not change in the control group [47]. The previous studies suggest that colchicine is more effective in PFAPA patients who had *MEFV* variants compared to those without *MEFV* variants [41, 43, 53]. Dusser et al. [53] also demonstrated that oral aphthosis and chronic fatigue were less common among colchicine-responder PFAPA patients compared to non-responders. There are no studies about the optimum duration of colchicine treatment in PFAPA. In the presented case, colchicine treatment could be discontinued if the patient is asymptomatic with normal inflammatory markers for at least 2 years as previously proposed for heterozygote FMF patients [54]. However, close follow-up should be warranted after cessation the treatment, since the patient is heterozygous for an exon 10 *MEFV* mutation.

It may be argued that the diagnosis was FMF instead of PFAPA in this patient. However, PFAPA diagnosis depends on several features: the presence of only the core symptoms of PFAPA during attacks both before and after tonsillectomy, the absence of signs and symptoms of serositis or arthritis during attacks, remission for 3 years after tonsillectomy, and history of PFAPA cured after tonsillectomy in a first-degree relative. Furthermore, despite fulfilling the pediatric FMF criteria [55], the patient did not meet the Tel-Hashomer criteria for FMF diagnosis [56] before tonsillectomy. Only after tonsillectomy and responding to colchicine treatment, there would be a "probable" FMF diagnosis according to the Tel-Hashomer criteria [56]. M694V heterozygosity, response to colchicine, and lack of cure with tonsillectomy could be evaluated in favor of FMF diagnosis. However, there are previous reports of PFAPA patients who were heterozygous for M694V mutation and responded to colchicine especially in cohorts from FMF-endemic areas such as Israel or Turkey [33, 39, 41, 43, 46, 47].

It may be difficult to dissect PFAPA diagnosis from FMF diagnosis in *MEFV* mutation carriers, especially in FMF-endemic areas [57]. In general, the presence of periodicity (clock-work regularity of attacks), the involvement of upper respiratory tract, the absence of serositis symptoms, and response to single-dose corticosteroids during attacks are in favor of PFAPA diagnosis rather than FMF [57, 58]. In addition, *MEFV* mutations could be checked in PFAPA patients if the patient has symptoms not typical for PFAPA (such as severe abdominal pain, arthralgia/arthritis, and chest pain), does not respond to corticosteroids during attacks, does not respond to tonsillectomy, and if the disease is not self-limited in the long term [2, 57, 58]. Some patients, especially ones with symptoms of serositis in several attacks, were considered to have both PFAPA and FMF in the literature [40]. Butbul-Aviel et al. demonstrated that abdominal pain, myalgia, and arthralgia were more frequent during attacks in PFAPA/FMF patients compared to only-PFAPA patients [40]. For the presented patient, we should also mention that it is not possible to totally exclude monogenic autoinflammatory diseases or the cumulative effect of different mutations on different genes without performing extensive genetic analysis.

There are a few limitations of this study. There may be recall bias about the attack-free period after tonsillectomy, since the patient did not see a physician regularly, as they thought that the disease was cured. Since there is no standard definition for remission after tonsillectomy, some patients with recurrence of disease after a period of remission could have been classified merely as being tonsillectomy refractory in the literature. This might have led to the underrepresentation of patients with a similar phenotype in the literature.

Conclusion

Albeit rarely, relapses of PFAPA syndrome could be observed after tonsillectomy. The presence of such patients opposes with the hypothesis that the trigger or immune dysregulation in PFAPA pathogenesis resides in tonsils. Increasing number of reports on diverse disease manifestations in PFAPA could give us further clues about the disease etiopathogenesis. The physicians could perform tests to exclude monogenic autoinflammatory diseases (especially in areas endemic for certain monogenic autoinflammatory diseases such as eastern Mediterranean countries endemic for FMF) in the patients with relapse after remission with tonsillectomy, since the results may guide the treatment which was the case for the presented patient. However, the cost-effectiveness of these genetic tests should be considered carefully.

Author contribution EDB designed the structure of the article, EDB and HBB performed the literature review, drafted and critically revised the text, and approved the final version of the manuscript.

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Compliance with ethical standards

No part of the manuscript including the table and figure were published elsewhere.

Conflict of interest The authors declare no conflict of interest.

Informed consent Written informed consent was obtained from the presented patient and his parents.

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