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Tonsillectomy as a Treatment for Psoriasis: A Review

Wiggin Wu^{1,2,*}, Maya Debbaneh^{1,3,*}, Homayoun Moslehi¹, John Koo¹, and Wilson Liao¹

¹Psoriasis and Skin Treatment Center, Department of Dermatology, University of California, San Francisco Medical Center, San Francisco, California, USA

²School of Medicine, University of California, San Diego, La Jolla, California, USA

³School of Medicine, University of California, Irvine, Irvine, California, USA

Abstract

Psoriasis is a chronic skin disorder that affects 1% to 3% of the general population worldwide. Streptococcal infection, especially streptococcal pharyngitis, has been shown to be a significant trigger of psoriasis in some patients, possibly by sensitizing T cells to keratin epitopes in the skin. Due to the role of the palatine tonsils as an immunological organ that may generate autoreactive T cells, tonsillectomy has been investigated as a treatment for psoriasis. Tonsillectomy originally gained acceptance in Japan as a treatment for palmoplantar pustulosis, a condition that shares features with pustular psoriasis. Subsequently, tonsillectomy has been used for the treatment of plaque psoriasis and guttate psoriasis. Recently, the first randomized, controlled clinical trial of tonsillectomy was performed. Here, we review the available evidence for the benefit of tonsillectomy as a treatment for palmoplantar pustulosis and psoriasis. We also discuss molecular studies aimed at understanding the role of tonsils in skin disease.

Keywords

psoriasis; palmoplantar pustulosis; tonsillectomy; tonsil

Introduction

Psoriasis is a chronic, immune-mediated, inflammatory skin disorder that affects about 1% to 3% of the general population worldwide (1). There are five sub-types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic, with the most common sub-type being plaque psoriasis. Because psoriasis is most often chronic, or can recur intermittently, psoriasis imposes a large psychosocial and financial burden on patients (1). The pathogenesis of psoriasis comprises the interaction between genetics and environmental factors such as infection, stress, injuries, cigarette smoking, obesity and medications such as lithium, NSAIDs, and others (2–4). Group A streptococcal infection has been shown to be the most

Corresponding Author: Wilson Liao, MD, UCSF Psoriasis and Skin Treatment Center, 515 Spruce St., San Francisco, CA 94118, (415) 476-8364, liaowi@derm.ucsf.edu.

*These authors contributed equally to this manuscript.

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compelling infectious factor, as it has long been known that patients with psoriasis can have recurrence or worsening of disease after an upper respiratory infection or sore throat (5, 6). As psoriasis is known to be a T-cell mediated disease, it has been proposed that certain T cells primed against streptococcal M proteins in the tonsils may cross-react with epitopes from human keratins to cause exacerbations of psoriasis (7). Although not well studied, some reports have indicated that tonsillectomy may be effective for the treatment for psoriasis. The majority of these studies have been performed in patients with palmoplantar pustulosis, a clinical entity considered by some practitioners as a variant of pustular psoriasis. Tonsillectomy has also been examined as a treatment for chronic plaque psoriasis and acute guttate psoriasis in several case reports and case series. This review synthesizes the reported studies of tonsillectomy as treatment for psoriasis to clarify its efficacy for use in psoriasis.

Methods

The PubMed database was searched for English-language articles using the keyword “psoriasis and tonsillectomy” between the date ranges 1960 to 2012. Only primary sources (clinical trials, case series, and case reports) were included in the study. Additional references were obtained by examining the citations of the identified papers. A total of 13 articles met inclusion criteria, including eight case series, four case reports, and one clinical trial.

Results

We identified seven clinical reports of tonsillectomy in palmoplantar pustulosis, one report in generalized pustular psoriasis, three reports in plaque psoriasis, and three reports in guttate psoriasis. Below we examine the results of tonsillectomy in each psoriasis subtype, and the results are summarized in Table 1.

Palmoplantar pustulosis (PPP)

PPP is characterized by the development of recurrent crops of sterile pustules on the palms and soles, surrounded by scaly and erythematous skin that may fissure. Histologically, PPP shows an intra-epidermal collection of neutrophils and a mixed perivascular and diffuse infiltrate of inflammatory cells in the upper dermis. The relationship between PPP and psoriasis is still under investigation (8). Patients with PPP may have extra-palmoplantar lesions that resemble psoriasis. Conversely, patients with generalized pustular psoriasis (GPP), who present with large areas of pustulosis on the trunk and extremities and signs of systemic inflammation such as fever and leukocytosis, may have pustular lesion on the palms and soles that are histologically identical to PPP. Recently, rare pathogenic variants in the *IL36RN* gene have been found in both PPP and GPP patients, suggesting that these two disorders may share a common genetic and immunologic basis (9).

PPP may be exacerbated by acute tonsillitis and use of tonsillectomy to treat PPP has been largely pioneered in Japan. Takahara et al. published a case series reporting an improvement in skin lesions in 87% of PPP patients (n = 47) at 12 months following tonsillectomy (10) (Table 1). The group then reported a prospective case series of 116 patients undergoing

tonsillectomy for the treatment of PPP (11). Results indicated that 109 out of 116 patients (94%) showed improvement by subjective self-assessment and 52 of 59 patients (88%) by objective Palmoplantar Pustulosis Area and Severity Index (PPPASI) scoring.

In a 2005 retrospective study by Yokoyama et al., questionnaires were sent to 95 PPP patients who underwent tonsillectomy between 1983 and 1995. A valid response rate of 65% was obtained and based on patient assessment and the frequency of visits to a dermatologist, 89% subjectively showed marked improvement or complete remission after tonsillectomy (12). Similarly, Ueda et al. published a case series of 15 patients who were clinically assessed using a 10-point scale by a dermatologist three months following tonsillectomy. Thirteen of 15 patients (87%) reported anywhere from an effective to complete response to tonsillectomy, while only one patient reported a partial response and one patient reported no response (13). Using the same efficacy scale, Yoshizaki et al. examined 14 dermatologist-diagnosed PPP patients. This patient cohort was enriched for cases in which tonsillitis may have served as a trigger of skin disease, as 9 of the 14 patients reported multiple episodes of acute tonsillitis and 8 of these patients had exacerbations of psoriasis during tonsillitis episodes. Twelve of the 14 patients reported an effective to complete response to tonsillectomy, two patients reported a partial response, and zero patients reported no response (14). The therapeutic effect of tonsillectomy has also been examined in generalized pustular psoriasis (GPP), which shares clinical and histologic features with PPP. Ozawa et al examined 385 Japanese patients with GPP; of the 12 GPP patients who received tonsillectomy, the procedure was effective in 2 patients (16.7%) although approximately 50% showed a decrease in pustular lesions (15).

PPP can be seen as a part of syndromic disorders such as SAPHO (Synovitis, Acne, PPP, Hyperostosis, and Ostitis). Interestingly, tonsillectomy has been reported to improve the extracutaneous and cutaneous manifestations of some of these PPP-associated disorders. Noda et al. described a 53-year-old man with a 3-year history of PPP, IgA nephropathy, and sternocostoclavicular hyperostosis (SCCH). After tonsillectomy, all the symptoms of IgA nephropathy, PPP and SCCH were alleviated within six months (16). Sakiyama et al. described 3 patients with PPP whose symptoms of arthro-osteitis improved after tonsillectomy (17). Tsuboi et al. also reported a 50 year-old female with PPP and a history of sternoclavicular joint pain whose cutaneous lesions improved after tonsillectomy (18).

Several groups have performed molecular studies to investigate why tonsillectomy might be effective in PPP. Ueda et al. found that expression of beta-1 integrin, an adhesion molecule important for cell-cell and cell-matrix interactions, was higher on both tonsillar and peripheral blood CD4-positive T cells in PPP patients compared to non-PPP patients ($P < 0.001$). They showed that only in PPP patients, beta-1 integrin expression on tonsillar CD4-positive T cells was significantly enhanced after in-vitro stimulation with B-streptococcal antigen ($P < 0.05$). Tonsillar CD4-positive T cells of PPP patients also showed better chemotactic response to the beta-1 integrin ligand than those of non-PPP patients ($P < 0.05$). Therefore, it is proposed that the PPP patients may benefit from tonsillectomy as it reduces the overall percentage of beta-1 integrin-positive CD4-positive T cells (13).

Similarly, Yoshizaki et al. found that expression of the chemokine receptor CCR6 on both tonsillar and peripheral blood T cells was upregulated more in PPP patients than in non-PPP patients ($P < 0.001$). They also showed that in PPP patients CCR6 expression on tonsillar T cells was significantly enhanced after in-vitro stimulation with alpha-streptococcal antigen ($P < 0.05$), but this was not observed in non-PPP patients. These results suggest that an immune response to alpha-streptococci may enhance CCR6 expression on T cells in tonsils and that CCR6-positive T cells may move to the peripheral blood circulation, resulting in recruitment to target skin lesions in PPP patients (14). While there are many proposed pathways and factors in the theory behind how tonsillectomies may affect PPP, the complete pathophysiology is still not well understood and further research is still needed.

Chronic plaque psoriasis

Chronic plaque psoriasis is characterized by round, circumscribed, erythematous plaques with an overlying silvery-white scale located most commonly on the scalp, extensor surfaces of limbs, elbows, knees, umbilical, and sacral region. Chronic plaque psoriasis is present in up to 80 to 90% of people with psoriasis.

Thorleifsdottir et al. performed the first randomized clinical trial of tonsillectomy in plaque psoriasis. Twenty-nine patients with dermatologist-diagnosed chronic plaque psoriasis were recruited and randomly assigned into the tonsillectomy ($n=15$) or control ($n=14$) group. Notably, patients were included in the study only if they had a history of psoriasis exacerbation after upper respiratory infections. After tonsillectomy, their disease course was followed for at least two years and disease severity was assessed by an observer-blinded dermatologist using the Psoriasis Area and Severity Index (PASI). The results showed that 86% of patients receiving tonsillectomy showed a significant reduction in the PASI ranging from 30–90%, whereas no improvement in the PASI was seen in controls ($p<0.001$). A majority of tonsillectomy patients (60%) also reached a 50% reduction in skin lesions. Most patients saw improvement at two months and maintained improvement for two years (7).

In another uncontrolled case series, Hone et al. found that among seven patients with plaque psoriasis, two (29%) were cleared, two (29%) were improved and three (42%) were unchanged (19). Nyfors et al. performed a retrospective analysis of 74 plaque psoriasis patients (18 males and 56 females, age range 4 to 33 years) in Denmark who underwent tonsillectomy. Subjects answered questionnaires regarding their psoriasis and 32% subjectively reported clearance after tonsillectomy, 32% reported marked improvement, 39% reported some improvement, 22% reported no improvement, and 7% reported worsening (20). The authors further examined whether clinical or demographic variables might predict which patients would respond to tonsillectomy. Surprisingly, among the 66 study participants who reported one or more episodes of tonsillitis in the years preceding the tonsillectomy, there was no statistical difference in the benefit of tonsillectomy for patients who reported that their tonsillitis flared their psoriasis versus patients who reported that tonsillitis had no effect on their psoriasis. Similarly, the benefit of tonsillectomy was not found to be statistically correlated with gender, age, duration of psoriasis, or number of tonsillitis episodes, although statistical power was limited (20).

The immunological role of the palatine tonsils in relation to plaque psoriasis was studied by Thorleifsdottir et al. (7). They showed that there was a close correlation between the degree of clinical improvement in individual patients receiving tonsillectomy and reduction in the frequency of streptococcal and keratin peptide-reactive IFN- γ -positive CD8-positive skin-homing T cells in their circulation. These findings indicate that the palatine tonsils may generate effector T cells that recognize keratin peptides in the skin and worsen psoriasis. With removal of the tonsils, the subsequent decrease in skin-homing T cells may result in improvement of chronic plaque psoriasis.

Guttate psoriasis

The strongest clinical correlation between streptococcal pharyngitis and exacerbation of psoriasis occurs with guttate psoriasis, a distinctive form of psoriasis characterized by the acute onset of numerous discrete erythematous lesions 2 to 5 mm in diameter over the trunk and extremities. It occurs mostly in patients under age 30 and recurrent episodes are common. Despite the strong clinical association between streptococcal infection and guttate psoriasis, there are surprisingly few published reports describing the effect of tonsillectomy in this psoriasis subtype.

McMillin et al. reported 2 cases of recurrent guttate psoriasis that cleared after tonsillectomy. An eleven year-old boy and a five year-old girl both showed 100% improvement 1 to 2 months after tonsillectomy and remained clear at 16 months (21). In another retrospective case series, Hone et al. found that five of six (83%) patients with guttate psoriasis cleared completely after tonsillectomy and one had subjective improvement. Patients were followed by regular outpatient dermatology follow-up and questionnaires (19). A study of two Japanese sisters ages 7 and 11 with guttate psoriasis reported 100% clearance of the psoriasis within two and six months after tonsillectomy, respectively. Of note, the two sisters also had a history of proteinuria that was also cleared after tonsillectomy (22).

Discussion

Review of the literature suggests that tonsillectomy may be of considerable benefit for certain patients with palmoplantar pustulosis (PPP), plaque psoriasis, and guttate psoriasis. The largest group of patients for which published data are available is PPP, with over 280 total tonsillectomy cases reported (Table 1). The data for PPP are limited to case series and case reports, which lack rigorous control groups and which may be susceptible to reporting bias. Nevertheless, the high rate of reported response to tonsillectomy in PPP, generally greater than 80% in individual studies (Table 1), suggests that tonsillectomy may be an effective treatment option for this disorder. Beneficial results have been primarily reported in the Japanese population; thus, additional studies are needed in other ethnic populations. Molecular studies of PPP suggest that tonsillar and peripheral blood CD4-positive T cells in patients with PPP recognize streptococcal antigens and express higher amounts of immune markers such as beta-1 integrin and CCR6. This provides a biologically plausible model for the benefit of tonsillectomy in PPP. There is debate as to whether PPP is related to psoriasis or represents a distinct clinical entity (8). Rare variants in *IL36RN* gene have been identified

in both PPP and generalized pustular psoriasis (GPP) (9). It is therefore noteworthy that in the one and only study we could identify for GPP, involving twelve patients treated by tonsillectomy, 16.7% of patients showed an effective response and 50% showed decrease in pustular lesions (15).

For plaque psoriasis, there are a little over 100 cases of tonsillectomy reported in the literature, fewer than in PPP. The response rate in the two largest studies of plaque psoriasis ranged between 71% and 86% (Table 1). To date, the only randomized, controlled clinical trial of tonsillectomy for psoriasis was conducted in patients with plaque psoriasis. That trial, containing 29 patients, showed an overall beneficial effect of tonsillectomy in the treatment group but no improvement in the control group ($p < 0.001$) (7). The reduction in psoriasis severity in tonsillectomy patients was maintained over two years. Furthermore, the improvement in psoriasis was significantly correlated with the reduction in the frequency of autoreactive, skin-homing CD8-positive circulating T cells, suggesting a mechanistic explanation for why tonsillectomy was beneficial.

Although the most well known clinical association between psoriasis and streptococcal pharyngitis occurs with guttate psoriasis, we identified only 10 published cases of guttate psoriasis treated with tonsillectomy (Table 1). In all 10 cases, a complete clearing or significant clearing of the psoriasis was reported. With such limited numbers, it is difficult to draw more definitive conclusions on the benefit of tonsillectomy in this group, although the high response rate is interesting and suggests the importance of further study.

An important clinical question is whether certain factors beyond psoriasis subtype might predict which psoriasis patients are likely to benefit from a tonsillectomy. For example, it might be expected that patients who report a history of psoriasis exacerbation with tonsillitis might respond better to tonsillectomy than psoriasis patients who do not flare with episodes of tonsillitis. However, a retrospective study of 74 plaque psoriasis patients undergoing tonsillectomy did not find a statistically significant difference in benefit of tonsillectomy between these two groups. Additionally, the benefit of tonsillectomy was not found to be linked to gender, age, duration of psoriasis, or number of tonsillitis episodes (20). Further research is needed to identify which groups of psoriasis patients are likely to respond best to tonsillectomy.

Clinical recommendation of tonsillectomy for the treatment of palmoplantar pustulosis or psoriasis should be made in the context of understanding the other indications and risks of this surgical procedure. In adults, the most common indications for tonsillectomy are chronic or recurrent infection (57%) or upper airway obstruction due to tonsillar hypertrophy (27%) (23). Other indications may include obstructive sleep apnea, asymmetric tonsils, halitosis, peritonsillar abscess, or infectious mononucleosis (24). In children, the most common indications include recurrent acute throat infections, chronic tonsillitis, pharyngitis, and chronic carriage of group A beta-hemolytic Streptococci (25). Potential significant peri-operative complications of tonsillectomy include pain and post-operative bleeding. Post-operative bleeding occurs in 3 to 6% of patients with approximately 50% of these patients requiring transoral control of bleeding in the operating room (26, 27). Significant throat pain is to be expected, but may not occur until one to two days after the

surgery. Patients may also have referred ear pain from manipulation of the glossopharyngeal nerve. True post-operative tonsillar bed infection is rarely seen after tonsillectomies. Other complications include local injuries such as soft tissue injury, chipped teeth, temporomandibular joint dislocation, or atlantoaxial instability. Most individuals undergoing tonsillectomy are able resume light activity within two weeks.

Conclusion

The combined reports from the literature suggest that tonsillectomy can be an effective treatment for palmoplantar pustulosis, plaque psoriasis, and guttate psoriasis. Because nearly all studies were limited to case reports and case series, the strength of evidence is limited. However, one randomized, controlled clinical trial of tonsillectomy in 29 patients with plaque psoriasis showed a significant benefit to tonsillectomy that was sustained over a two-year follow-up period. Molecular studies have provided evidence that the tonsils harbor autoreactive T cells that can enter the circulation and home to the skin. Therefore, tonsillectomy appears to reduce the frequency of these autoreactive cells. Further studies are needed to clarify exactly which psoriasis patients are most likely to benefit from this surgical procedure.

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Table 1
Summary of studies of examining the effect of tonsillectomy in palmoplantar pustulosis (PPP) or psoriasis.

Study	Year	Country	Disease	Study Design	Number	Gender	Age Range	Results	Follow-up
Yokoyama et al. (12)	2004	Japan	PPP	Case series	95	36M, 59F	21-72, mean 41.2	88.7% subjectively showed marked improvement or complete remission.	>5 years
Takahara et al. (10)	2005	Japan	PPP	Case series	47	14M, 23F	21-74, mean 49	87% of patients showed improvement in psoriasis lesions at 12 months after tonsillectomy.	none
Tsuboi et al. (18)	2006	Japan	PPP	Case report	1	1F	50	Psoriasis lesions improved after tonsillectomy.	none
Noda et al. (16)	2007	Japan	PPP	Case report	1	1M	53	All the symptoms of PPP, IgA nephropathy, and SCCH were alleviated 6 months after the tonsillectomy.	6 months
Ueda et al. (13)	2010	Japan	PPP	Case series	15	4M, 11F	23-56, median 43	13 patients classified as effective or better; 1 patient partially effective, 1 patient not effective.	none
Takahara et al. (11)	2011	Japan	PPP	Case series	116	N/A	N/A	94% of patients reported subjective improvement; 88% of patients improved by Palmoplantar Pustulosis Area and Severity Index (PPPASI) scoring.	none
Yoshizaki et al. (14)	2011	Japan	PPP	Case series	14	2M, 12F	27-67, median 44	12 patients classified as effective or better, 2 patients partially effective.	none
Ozawa et al. (15)	1999	Japan	GPP	Case series	385 (12 treated)	N/A	N/A	Tonsillectomy effective in 16.7% of cases, 50% of cases showed decrease in pustular lesions.	none
Nyfors et al. (20)	1976	Denmark	Plaque	Case series	74	18M, 56F	4-33	32% cleared, 39% improved, 22% no benefit, 7% had disease worsening	5 years
Thorleifsdottir et al. (7)	2012	Iceland	Plaque	Randomized clinical trial	29 (15 treated, 14 untreated)	3M, 12F	24-45, mean 35.3	86% showed sustained improvement after tonsillectomy ranging from 30 to 90% reduction in disease severity (PASI score); 60% reached 50% reduction in skin lesions. (p < 0.001).	2 years

Study	Year	Country	Disease	Study Design	Number	Gender	Age Range	Results	Follow-up
Hone et al. (19)	1996	Denmark	Plaque and Guttate	Case series	13 (6 guttate, 7 plaque)	1M, 12F	6-28, mean 17	53% cleared, 23% improved, 24% no benefit, 0% had disease worsening	26 months
Saita et al. (22)	1979	Japan	Guttate	Case report	2	2F	7 and 11	Psoriasis and proteinuria cleared within 2 months	none
McMillin et al. (21)	1999	United States	Guttate	Case report	2	1M, 1F	11 and 5	100% showed marked improvement 1-2 months post-tonsillectomy; 100% of patients cleared at 16 months	16 months