Psoriasis is associated with fissured tongue but not geographic tongue: a prospective, cross-sectional, case-control study

Babak Monshi1, Sofia Grabovac1, Lilli Gulz1, Christina Ellersdorfer1, Marin Vujic1, Leo Richter1, Danijel Kivaranovic2, Klemens Rappersberger1,3, Igor Vujic1,3

(1) Department of Dermatology, Venereology and Allergology, Teaching Hospital of the Medical University Vienna, Vienna, Austria
(2) Department of Statistics and Operations Research, University of Vienna, Vienna, Austria
(3) Sigmund Freud University Vienna, School of Medicine, Vienna, Austria

Introduction

Psoriasis, a frequent, chronic inflammatory skin disease affecting 1–3 % of the world’s population, is associated with multiple comorbidities such as arthritis and metabolic disorders, might impair patients’ quality of life and has a substantial socio-economic impact [1, 2]. For some time, it has been a matter of debate whether psoriasis might affect mucosal surfaces in the oral cavity and whether “oral psoriasis” exists [1–6]. In particular, the association of psoriasis with two specific lesions of the tongue, namely geographic tongue (GT) and fissured tongue (FT), has been the focus of research [7–16].

Geographic tongue or benign migratory glossitis (lingua geographica) is an inflammatory oral lesion of unknown etiology with reported prevalence rates from 1–9 % [16, 17]. Clinically it is characterized by chronic, recurrent, mostly asymptomatic, migrating, circinate erythematous patches with whitish borders on the lateral and dorsal aspects of the tongue (Figure 1a) [17, 18]. The histology of GT is somewhat reminiscent of psoriasis with neutrophilic exocytosis and spongiotic pustules in the surface epithelium of the tongue. However, biopsy is usually not required as relevant differential diagnoses such as oral candidiasis, tongue conditions due to nutritional deficiencies such as iron or vitamin B12 deficiency, oral lichen planus, lichenoid mucosal reactions to...
amalgam or drugs and other forms of leukoplakia including oral hairy leukoplakia and premalignant conditions can be accurately distinguished on clinical grounds [17]. Geographic tongue has been associated with a variety of diseases such as atopic dermatitis, diabetes, reactive bronchitis, anemia, stress, hormonal disturbances, Reiter’s and Down’s syndromes, lithium therapy and psoriasis [7–9, 11, 13, 14, 16, 18–20]. Nevertheless, some reports have contradicted the association of psoriasis and GT [16, 18, 19].

The second type of tongue lesion, FT (lingua plicata), has reported prevalence rates of 5–11 % and is clinically characterized by a longitudinal groove on the back of the tongue sometimes associated with lateral furrows (Figure 1a). The prevalence of FT increases with age and the usually asymptomatic condition does not require treatment unless local irritation due to food debris or bacterial overgrowth occurs. Like GT, FT has also been associated with psoriasis but also with other conditions such as Down’s syndrome, acromegaly, Melkersson-Rosenthal syndrome and GT itself [21, 22].

The rationale for our study was that prevalence rates of GT and FT vary greatly across geographic regions and between different ethnic groups as is the case for psoriasis [16, 19, 22, 23]. Indeed, most of the available evidence on the association of GT and FT with psoriasis was generated in non-European countries with different ethnic makeup compared to Central Europe [7–16]. We therefore conducted a prospective, case-control study to evaluate the prevalence of GT and FT in a cohort of Austrian patients with psoriasis as well as in a healthy control group.

Material and Methods

This study was approved by the ethics committee of the city of Vienna (EK 18-235-VK) and describes a prospective, epidemiologic, cross-sectional (single-visit), single-center, case-control study of the prevalence of GT and FT in a cohort of patients with psoriasis and in a healthy control group. Consecutive patients from September 2017 until July 2018 with psoriasis diagnosed and treated at the outpatient clinic for immunodermatological diseases at the Department of Dermatology, Venereology and Allergology, Klinik Landstraße, Vienna, Austria, willing to participate in the study were included. Subjects in the control group were volunteers without a history of psoriasis or psoriatic arthritis. Exclusion criteria were age < 18 years and lack of consent. Patients were assessed using a case-report form regarding age, sex, smoking-habits, concomitant skin diseases particularly atopic dermatitis, history and type of allergies, duration and onset of psoriasis (early onset = diagnosis before or at the age of 40, late onset = diagnosis after the age of 40, respectively), momentary disease severity according to the Psoriasis Area and Severity Index (PASI), psoriatic nail involvement, psoriatic arthritis and psoriasis-specific therapy at the time of the survey. In a second step all participants underwent systematic oral mucosal examination performed by two dermatologists, I.V. and L.R., using artificial light, gloves and a wooden spatula. Geographic tongue and/or FT were only diagnosed in unambiguous cases and diagnosis was based on the typical clinical presentation of GT and FT, respectively (Figure 1a, b) [16, 17, 22].

Continuous variables were expressed as median with interquartile range (IQR) in parenthesis and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as absolute and relative frequencies and compared by the chi-squared test. A sample size of 173 was calculated based on data from previous studies available at that time (effect size = 0.1 and df = 1 for chi-squared test) with a significance level of 5 % and power of 80 % [7, 8, 10, 13, 15, 24]. P values < 0.05 were considered statistically
significant and statistical analysis was performed using R version 3.4.4.

Results

We included 346 participants in the study, 173 patients with plaque psoriasis and 173 non-psoriatic volunteers. No patient had pustular, guttate or isolated palmoplantar or inverse psoriasis. Patients with psoriasis, 58 women and 115 men, had a median age of 50 years (37–60) and healthy volunteers, 79 women and 94 men, had a median age of 54 years (43–64) (Table 1). Overall, 95 study participants had a history of type 1 and/or type 4 allergies, 42 in the psoriasis group (24 %) and 53 in the control group (31 %). Detailed analysis of the type of allergies in each group is depicted in the online supplementary material and the most prevalent allergies were those to grass pollen and mugwort pollen, respectively (Figure 1, online Supporting Information). Characteristics of patients with psoriasis are provided in Table 1. In detail, median onset of psoriasis was at the age of 26 (12–40) years and 131 patients had an early onset before the age of 40 years while 42 had a late onset after the age of 40 years. Median duration of psoriasis at the time of the study was 20 years (10–27) and the median PASI score was 2 (0–4.1). As described previously, we categorized patients with psoriasis according to their PASI scores at the time of the study into clear of skin lesions (PASI = 0), mild (PASI 1–10), moderate (PASI 11–30) and severe (PASI > 30) disease activity [25]. Out of a total of 173 patients, 48 patients had no skin lesions, 111 had a mild and 14 patients had a moderate form of psoriasis. No patient had severe disease extent at the time of the study. Overall, 165 of 173 psoriasis patients were under therapy and detailed analysis of anti-psoriatic therapy is depicted in the supplementary material (Figure 2, online Supporting Information). In brief, most patients received ustekinumab (n = 47) followed by methotrexate (n = 29) and adalimumab (n = 22).

GT was present in eight study participants, of which four had psoriasis and four were healthy volunteers, corresponding to a prevalence of 2.3 % in both groups (Figure 2a, Table 2). FT was present in 38 participants, of which 25 had psoriasis and 13 were healthy controls, corresponding to a prevalence of 14.4 % and 7.5 %, respectively (Figure 2, Table 2). Univariate analysis revealed that GT was significantly associated with smoking habits (P = 0.01) and FT with psoriasis (P = 0.04). No associations of GT and FT were found with other psoriasis-specific parameters including disease onset or PASI scores (Table 3).

Discussion

It has been published that GT and FT are associated with psoriasis [7, 9, 14, 16, 24, 26]. Furthermore, it has been speculated that GT, due to its histological resemblance with psoriasis, might constitute a form of “oral psoriasis”, a notion which has recently been supported by a meta-analysis [16, 27]. On the other hand, a few but large prevalence studies failed to find any association between GT and skin diseases such as psoriasis or atopic dermatitis. In addition, there is evidence that the prevalence of GT and FT might differ between geographic regions and various ethnic groups [18, 19, 22].

In this prospective, cross-sectional, case-control study we investigated the prevalence of GT and FT in 173 patients with psoriasis vulgaris treated in a tertiary referral center in Vienna, Austria, and compared them to a cohort of 173 healthy individuals. We herein found an equal point-prevalence of GT in both groups of our cohort (four patients [2.3 %] in each group) and thus no evidence of an association between the two entities (Figure 2a, Table 2). Our findings are somewhat surprising as most comparable case-control studies

| Table 1 Patients’ general and psoriasis-specific characteristics. |
|---------------------------------|----------------|----------------|
|                                | Psoriasis | Healthy control |
|--------------------------------|-----------|----------------|
| (total n = 346)                | (n = 173) | (n = 173)       |
| Median age, years (IQR)        | 50 (37–60)| 45 (43–64)      |
| Sex, No.                       |            |                |
| male                           | 115       | 94             |
| female                         | 58        | 79             |
| Smoking habits, No.             |            |                |
| smoker                         | 64        | 50             |
| non-smoker                     | 109       | 123            |
| Allergies, No.                 |            |                |
| yes                            | 42        | 53             |
| no                             | 131       | 120            |
| Onset of psoriasis             |            |                |
| Median age, years (IQR)        | 26 (12–40)| n.a.           |
| min                            | 0         |                |
| max                            | 75        |                |
| PASI                           |            |                |
| Median (IQR)                   | 2 (0–4.1)| n.a.           |
| max                            | 25        |                |
| min                            | 0         |                |
| Nail psoriasis, No.            | 105       | n.a.           |
| Psoriatic arthritis, No.       | 59        | n.a.           |

*Abbr.: IQR, interquartile range; No., number of patients; n.a., not applicable.*
reported an association of GT with psoriasis with prevalence rates ranging from 5.67 % to 18.1 % (mean = 10.13 %) in the psoriasis group [16, 18, 19]. We can only speculate about the underlying reasons for this discrepancy. As there is evidence for a genetic background for both GT and psoriasis with well-documented associations with susceptibility regions such as PSORS1, HLA antigens or with specific mutations such as in the IL36RN gene, one explanation might be differences in the genetic makeup of studied cohorts [28–31]. Corroborating this hypothesis, the percentage of healthy volunteers with GT in our study was also low (2.3 %) compared to other studies in which prevalence rates of GT in control groups ranged from 0.88 % to 9 % (mean = 5.2 %) [16]. Thus, it is conceivable that different prevalence rates of GT between ethnicities and geographic regions might lead to divergent results in studies on the association of GT with psoriasis [16, 19, 22]. Another explanation might be that anti-psoriatic treatment, received by 159 out of 173 patients in our cohort as systemic therapy and leading to low overall PASI scores (median = 2 [0–4.1]), affected the prevalence of GT in our study (Table 1; Figure S2, online Supporting Information). While improvement of GT in the wake of anti-psoriatic treatment was described anecdotally in single case reports, large case-control studies and a recent meta-analysis found

Table 2 Univariate analysis of possible associations of geographic tongue (GT) and fissured tongue (FT) with patients’ general characteristics. Statistically significant results are depicted as bold numbers.

|                     | Overall  | No GT   | GT      | P value | No FT   | FT      | P value |
|---------------------|----------|---------|---------|---------|---------|---------|---------|
| Median age, years (IQR) | 51.5 (41–62) | 52 (41–62) | 44 (35–53.2) | 0.23    | 51 (40.8–62) | 54 (44.2–63) | 0.58    |
| Sex, No. (%)        |          |         |         |         |         |         |         |
| – Male              | 209 (60) | 203 (60) | 6 (75)  | 0.39    | 184 (60) | 25 (66) | 0.47    |
| – Female            | 137 (40) | 135 (40) | 2 (25)  |         | 124 (40) | 13 (34) |         |
| Smoking habits, No. (%) |        |         |         |         |         |         |         |
| – Smoker            | 114 (33) | 108 (32) | 6 (75)  | 0.01    | 98 (32)  | 16 (42) | 0.20    |
| – Non-smoker        | 232 (67) | 230 (68) | 2 (25)  |         | 210 (68) | 22 (58) |         |
| Allergies, No. (%)  |          |         |         |         |         |         |         |
| – yes               | 95 (27)  | 94 (28)  | 1 (12)  | 0.34    | 84 (27)  | 11 (29) | 0.83    |
| – no                | 251 (73) | 244 (72) | 7 (88)  |         | 224 (73) | 27 (71) |         |
| Psoriasis, No. (%)  |          |         |         |         |         |         |         |
| – yes               | 173 (50) | 169 (50) | 4 (50)  | 1       | 148 (48) | 25 (66) | 0.04    |
| – no                | 173 (50) | 169 (50) | 4 (50)  |         | 160 (52) | 13 (34) |         |

Abbr.: GT, geographic tongue; FT, fissured tongue; IQR, interquartile range; No., number of patients.
Table 3 Univariate analysis of possible associations of geographic tongue (GT) and fissured tongue (FT) with psoriasis-specific characteristics. No significant association was found.

|                        | Overall (n = 173) | No GT (n = 169) | GT (n = 4) | P value | No FT (n = 148) | FT (n = 25) | P value |
|------------------------|-------------------|-----------------|------------|---------|-----------------|------------|---------|
| Nail psoriasis, No. (%)| 108 (62)          | 106 (63)        | 2 (50)     | 0.60    | 95 (64)         | 13 (52)    | 0.24    |
| Psoriatic arthritis, No. (%)| 59 (34)          | 59 (35)        | 0 (0)      | 0.30    | 50 (34)        | 9 (36)    | 0.82    |
| Onset psoriasis, No. (%)|                  |                |            |         |                 |            |         |
| – late                 | 42 (24)           | 42 (25)        | 0 (0)      | 0.25    | 35 (24)        | 7 (28)    | 0.64    |
| – early                | 131 (76)          | 127 (75)       | 4 (100)    |         | 113 (76)       | 18 (72)   |         |
| PASI, Median (IQR)     | 2 (0–4)           | 1.8 (0–4)      | 5.5 (3.3–7.1) | 0.13    | 1.9 (0–4)      | 2 (0–4.3) | 0.76    |
| Psoriasis duration median years (IQR) | 20 (10–27) | 20 (10–27) | 14 (8.2–18.5) | 0.23 | 20 (10.8–28) | 14 (8–24) | 0.12 |

Abbr.: GT, geographic tongue; FT, fissured tongue; IQR, interquartile range; No., number of patients.

no evidence that prevalence rates of GT differ significantly between treated and non-treated psoriasis patients [7, 9, 16, 20, 32, 33]. Moreover, to date, controlled trials investigating the effect of systemic anti-psoriatic treatment on GT are lacking. Nevertheless, it needs to be stressed that in previous case-control studies anti-psoriatic treatment modalities were not further specified. Thus, it could be argued that they probably did not include as many patients as in our study who received biologicals such as interleukin-12/23 inhibitors (n = 48), interleukin-17 inhibitors (n = 31) and TNFα inhibitors (n = 31), as some of these compounds entered the market years after the mentioned studies were published (Figure S2, online Supporting Information) [7, 9, 20]. We therefore cannot completely refute the hypothesis that anti-psoriatic treatment might have improved our patients’ tongue conditions, and further studies including treatment-naïve psoriasis patients and longitudinal follow-up are needed to address this issue.

The question whether GT is a marker of psoriatic disease severity as measured by PASI remains to be fully elucidated. Some studies have reported a significant association of GT with high PASI scores, but this was not confirmed in other studies [8, 9, 12, 14, 34]. In our cohort, we also observed that psoriasis patients with GT had higher PASI scores (median = 5.5) than those without GT (median = 1.8). However, this difference was not statistically significant and possible explanations might be low overall numbers of GT and/or low overall PASI scores in our cohort as mentioned above (Table 3).

While further analysis revealed no associations of GT with sex, age, presence of allergies, duration and onset of psoriasis, nail psoriasis and psoriatic arthritis, it did reveal a significant association with cigarette smoking ($P = 0.01$) (Tables 2, 3). This finding is in contrast with other studies which reported either no differences in smoking habits or even a possible protective effect of smoking regarding the occurrence of GT [16, 24, 35]. In this regard it needs to be mentioned that comparability between our and previously published data is limited, as we and others did not evaluate details of smoking habits such as pack-years. In addition, our primary endpoint was the prevalence of GT in psoriasis and the total number of subjects with GT was low, potentially hampering this analysis.

In contrast to GT, we found a significant association of FT with psoriasis ($P = 0.04$), which is in line with published data (Figure 2b, Table 2) [7, 14, 20]. However, the rate of FT in our cohort, which was 7.5 % in healthy controls and 14.5 % in psoriasis patients, was also low compared to published figures that range from 9.5 % to 20.4 % in healthy controls and from 9.8 % to 47.5 % in psoriasis patients, respectively [7–10, 13, 14, 20, 24]. Similar to GT the etiology of FT remains unclear and the reasons for the association of FT with psoriasis are to be elucidated. It has been speculated that both conditions may share some common genetic background, result from a yet unknown interaction between two separate inflammatory processes, or a combination of both [7]. Some studies have shown that FT is associated with GT, non-smoking status, age over 21 years, onset of psoriasis after the age of 30 years as well as nail and genital involvement [7, 14, 19, 24]. In our cohort, we neither found a combination of GT and FT nor could we detect associations of FT with general parameters such as sex, age, smoking status, or presence of allergies or with psoriasis-specific factors such as onset and duration of psoriasis, PASI, nail involvement or psoriatic arthritis (Tables 2, 3).
The case-controlled design, strict diagnostic criteria and the analysis of anti-psoriatic treatment modalities are clear strengths of our study. However, some limitations warrant further discussion. First, the study was designed and powered to evaluate the prevalence of GT in patients with psoriasis, and other analyses such as the prevalence of FT in patients with psoriasis, or subgroup analyses, might be hampered by the low prevalence of both conditions in our cohort. Secondly, we cannot rule out a selection bias as this was a single center study including treated psoriasis patients who were recruited from a specialized outpatient clinic from a tertiary referral hospital. Thirdly, as GT is a chronic recurrent condition the study including treated psoriasis patients who were recruited we cannot rule out a selection bias as this was a single center hospital. Finally, we designed our study to ensure maximum comparability of our data [16].

In conclusion, we demonstrate in this prospective, cross-sectional, case-control study that the prevalence of GT in an Austrian cohort of 346 subjects was 2.3 % and thus lower than reported previously. More importantly, and in contrast to published data, we found no association of GT with psoriasis. Therefore, our study does not corroborate the hypothesis that GT is an oral manifestation of psoriasis. On the other hand, we found that FT was significantly associated with psoriasis, but whether both conditions are linked through common pathophysiological mechanisms remains to be elucidated.

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Correspondence to
Babak Monshi, MD
Department of Dermatology, Venereology and Allergology
Klinik Landstraße
Teaching Hospital of the Medical University Vienna
Juchgasse 25
1030 Vienna, Austria
E-mail: babak.monshi@wienkav.at

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