Facial Papules Are Early Sign of Frontal Fibrosing Alopecia: A Cross-Sectional Study

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Abstract: Frontal fibrosing alopecia (FFA), a form of lichen planopilaris (LPP), is primary cicatricial alopecia commonly affecting postmenopausal women. For the first time, we investigated the diagnosis of FFA and LPP in patients presenting with the chief complaint of facial papules and roughness. This cross-sectional was performed among 68 patients with facial papules. We described the epidemiology, comorbidities, clinical presentations, and the association between facial papules and LPP or FFA. All the patients were female with a mean age of 47.84 years. Scalp alopecia was observed in all the patients presenting with facial papules, of which 89.7% had FFA. Five patients were diagnosed with LPP without FFA. Most of the patients were premenopausal (73.5%), and 70.6% had grade I FFA. Concomitant cutaneous lichen planus involvement was observed more frequently than mucosal involvement. The most frequent comorbidities were hypothyroidism, dyslipidemia, and hypertension. History of alopecia areata was detected in 8.8% of the patients. Androgenetic alopecia (AGA) was present in 17 patients (25%). Facial papules are the silent and early signs of FFA and LPP. Paying attention to these early signs along with metabolic disturbances can help with the early diagnosis of the disease, especially among premenopausal women.

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Introduction

Lichen planus (LP) is a benign chronic and relapsing inflammatory disorder characterized by itchy, non-infectious rashes on the arms and legs. A form of LP with patchy hair loss, mainly on the scalp, is known as lichen planopilaris (LPP) (1). There are three forms of LPP distinguished by specific patterns, namely classic LPP, Lassueir Graham-Little Piccardi syndrome, and frontal fibrosing alopecia (FFA) (1,2).

FFA is a primary lymphocytic cicatricial alopecia, first described by Kossard in 1994 as a progressive symmetric marginal alopecia along the frontal and frontotemporal hairline (3). Considering the clinically significant inflammatory phenomenon and fibrosis, Olsen in 2005, proposed the term “cicatrical pattern hair loss” (4). The reported cases of FFA have markedly increased in recent years. FFA predominantly affects postmenopausal women; however, some cases of FFA have been reported among premenopausal women and rarely in men (5,6). The etiology of FFA remains conspicuous; however, hormonal factors and T-cell-mediated autoimmune reactions appear to play a predominant role in the pathogenesis of the disease (7).

Decreased or complete loss of the eyebrows occurs in 50-70% of cases (3). Loss of eyelashes and peripheral body hair (8) and mucous membrane (9) and nail involvement (10) are also occasionally present. Additionally, FFA, as a generalized inflammatory disorder, could be accompanied by autoimmune disorders such as autoimune thyroid disease, hypertension, coronary artery disease, and diabetes mellitus (11).

There are some recent reports on the concomitant occurrence of facial papules in 14-20% of patients.
Facial papules are early sign of frontal fibrosing alopecia

presenting as lichenoid inflammation of facial vellus hair, described by patients as roughening of facial skin (12). López-Pestaña, for the first time, described other facial lesions associated with FFA, including diffuse erythema, sometimes with a reticular pattern as a result of interfollicular lichenoid infiltrate and the gradual appearance of pigmented macules (13). It has been demonstrated that prominent sebaceous lobules with dilated ducts associated with an abnormal elastic framework lead to the formation of facial papules. Facial papules are claimed to be the late residual finding of an inflammatory process; thus, they could be seen early in the course of the disease (14). However, the presence of FFA in patients with characteristic facial papules and skin roughness, and most of the patients had not the previous diagnosis of FFA.

In this study, we sought to describe the comorbidities, clinical presentations, and the association between facial papules and LP or LPP and FFA to highlight the clinical importance of facial papules in the early diagnosis of FFA/LPP.

Materials and Methods

In this cross-sectional study, we enrolled all patients with the chief complaint of facial roughness and the presence of symmetrical facial skin-colored papules that were admitted to our clinic, from 2013 to 2018. All the participants were administered a 3-mm punch biopsy from scalp involvement, and 2.5 mm punch biopsy from facial papules for histological examination. The areas of the facial skin with more severe lesions were biopsied. The biopsy was done to confirm the diagnosis of a vellus hair lichen plan and excluded another popular cutaneous disease such as rosacea, seborrheic dermatitis, popular eczema, and acne. The patients were evaluated for the concurrent lichenplanopilaris, FFA, cutaneous or mucosal lichen planus disorders, eyebrow, eyelash, nail, axilla, and body hair involvement. If the alopecia was scarring, the biopsy was performed from these lesions as well. A board-certified dermatologist specializing in LPP and FFA assessed the included patients for typical clinical presentations and characteristic dermoscopy findings (15). In case of any frontotemporoparietal hair loss, the diagnosis of FFA was confirmed by histopathological examination of biopsies from the scalp representing primary scarring alopecia and clinical presentation like at least one of the following characteristics: eyebrow alopecia, interfollicular and perifollicular erythema, or perifollicular papules.

The clinical severity of FFA was classified based on a clinical scale measuring the area of cicatricial skin produced by the recession of the frontal and temporal hairline. This classification, as explained by Ceballos et al., (16), includes five severity grades as I (1 cm), II (1-2.99 cm), III (3.499 cm), IV (5.6.99 cm), and V (7 cm). The largest measure (frontal or temporal) is used to define the grade of severity.

Moreover, information like age, sex, smoking status, family history of the disease, age of menopause, age at onset of facial papules, comorbidities, and duration and extent of the disease were recorded.

All the patients were informed of the content and aims of the study and were ensured of the confidentiality of the data. Then, informed consent was obtained from all the patients. The study was approved by the Research Ethics Committee of Tehran University of Medical Sciences and performed in accordance with the declaration of Helsinki (No. IR.TUMS.VCR.REC.1397.573).

Statistical analysis

Statistical analysis was performed using the software SPSS 16.0.0 (SPSS, Inc., Chicago, IL, USA). Independent samples t-test and Chi-square tests were used for analyzing the collected data. The $P$ of less than 0.05 was considered as statistically significant.

Results

Data were gathered from 68 female patients with the mean age of 47.84 years (age range: 26-72 years; Table 1). There was a significant difference in the relative prevalence of the disease between premenopausal and postmenopausal women ($P<0.001$).

Skin biopsy was performed in all the patients with facial papules, FFA, and LPP (Figures 1 and 2).

![Figure 1. Facial papules: facial lesions as skin color symmetrical papules](image)

The histopathological examination of these facial lesions showed vellus hair involvement with the dense follicular lichenoid inflammatory process, vacuolar degeneration of the basal layer, and destruction of basal keratinocytes. Necrotic keratinocytes were found in both...
dermis and epidermis. Lymphocytic infiltrations were observed in infundibulum and isthmus, sparing the lower portions of the hair follicle (Figures 3 and 4). This examination showed LP with vellus hair involvement in all the 68 patients with facial papules.

Figure 2. Facial papules and frontal fibrosing alopecia: frontotemperoparietal recession and facial lesions as skin color symmetrical papules

Figure 3. Dense follicular lichenoid inflammatory process, vacuolar degeneration of the basal layer, and destruction of basal keratinocytes. (H&E *40)

Figure 4. Vacuolar degeneration of the basal layer and destruction of basal keratinocytes. Necrotic keratinocytes can be found both in the dermis and the epidermis. (H & E*100)

The mean time elapsed since the onset of facial papules and facial skin roughness was 2.11 years (range: 3 months to 6 years) prior to the visiting date. Positive family history and history of smoking were negative in all the patients (Table 2).

Scalp hair involvement was observed in all the patients, 34 (50%) of whom had LPP. 61 (89.7%) showed FFA, and 28 (40.5%) had both LPP and FFA (Table 1). Concomitant cutaneous LP was observed in eight patients, including three patients with dorsal hand and feet lesions and 5 (11.8%) patients with trunk involvement. Physical examination showed that none of the cases had nail involvement, 1 (1.5%) patient had mucosal involvement, and 51 (75%) patients had eyebrow involvement (Table 2).

Symptoms, including pruritus and trichodynia, were detected in 26 (38.2%) patients, and 2 (2.9%) patients had early menopause due to surgical cause. The most frequent comorbidities were respectively hypothyroidism in 18 (26.5%) patients, dyslipidemia in 10 (14.7%) patients, and arterial hypertension in 8 (11.9%) patients. A history of alopecia areata was detected in 6 (8.8%) patients. The incidence rate of hypertension was significantly higher in postmenopausal women than premenopausal ones (P<0.004).

Androgenic alopecia was present in 17 (25%) patients, and morphea and ichthyosis were detected in two patients (Table 2). In our study, 70.6% of the patients were in grade I, 19.1% were in grade II, 5.9% were in grade III, 1.5% were in grade IV, and 2.9% were in grade V FFA (Table 1). Finally, we did not find any association between the severity of FFA (grades III, IV, and V) and the duration of the diseases (P=0.481).

Table 1. Demographic characteristics of the study population and the prevalence of FFA and LPP.

|                          | Premenopausal women (n=50) | Postmenopausal women (n=18) | Total (n=68) | P    |
|--------------------------|-----------------------------|----------------------------|--------------|------|
| Mean age of onset        |                             |                            |              |      |
| I                        | 44.84±6.86                  | 58.84±5.83                 | 47.84±10.72  | <0.001|
| II                       | 36(72%)                     | 12(66.7%)                  | 48(70.6%)    |      |
|                          | 11(22%)                     | 2(11.1%)                   | 13(19.1%)    |      |
| Grade                    |                             |                            |              |      |
| III                      | 2(4%)                       | 2(11.1%)                   | 4(5.9%)      |      |
| IV                       | 0(0%)                       | 1(5.6%)                    | 1(1.5%)      |      |
| V                        | 1(2%)                       | 1(5.6%)                    | 2(2.9%)      |      |
| FFA                      | 44(88%)                     | 17(94.4%)                  | 61(89.7%)    | 0.666|
| LPP                      | 28(56%)                     | 6(33.3%)                   | 34(50%)      | 0.168|

The severity of alopecia: I (1 cm), II (1-2.99 cm), III (3-4.99 cm), IV (5-6.99 cm), and V (7 cm)
Facial papules are early sign of frontal fibrosing alopecia

Table 2. Clinical data of the study

|                                      | Premenopausal women | Postmenopausal women | Total     | P     |
|--------------------------------------|---------------------|----------------------|-----------|-------|
|                                      | 50 patients (73.5%) | 18 patient (26.5%)   |           |       |
| Eyebrow loss                         | 36(72%)             | 15(86.3%)            | 51(75%)   | 0.527 |
| Mucosal involvement                  | 1(2%)               | 0(0%)                | 1(1.5%)   | 1     |
| Axillary involvement                 | 1(2%)               | 1(5.6%)              | 2(2.9%)   | 0.462 |
| Body involvement                     | 4(8%)               | 4(22.2)              | 8(11.8%)  | 0.194 |
| Eyebrow involvement                  | 18(36%)             | 12(66.7%)            | 30(44.1%) | 0.030 |
| Itching                              | 18(36%)             | 8(44.4%)             | 26(38.2%) | 0.579 |
| AGA                                  | 14(28%)             | 3(16.7%)             | 17(25%)   | 0.527 |
| hypertension                         | 2(4%)               | 6(33.3%)             | 8(11.9%)  | 0.004 |
| Hyper lipedema                       | 8(16%)              | 2(11.1%)             | 10(14.7%) | 1     |
| hypothyroid                          | 12(24%)             | 6(33.3%)             | 18(26.5%) | 0.536 |
| hysterectomy                         | 2(11.1%)            | 0(0%)                | 2(2.9%)   | 0.067 |
| Alopecia areata                      | 2(4%)               | 4(22.2%)             | 6(8.8%)   | 0.038 |
| Duration of diseases                 | 2.11±.27            | 2.72±1.67            | 2.27±1.4  | 0.113 |

Discussion

Facial papules are among the facial lesions seen in FFA, reflecting lichenoid inflammation of facial vellus hair follicles. It suggests that the inflammatory process in FFA is systemic and not limited to the scalp (17). The involvement of vellus hair follicles as facial papules was first noted by Abbas et al., (2007) (3) in a 37-year-old premenopausal woman and later by Donati et al., (2011) (17) in four patients with typical clinical features of FFA. A recent study hypothesized that facial papules are a late residual finding of an inflammatory process (14). Signs of prior inflammation, such as pigment incontinence and destruction of elastic fibers, are seen in these lesions (14). However, there is a scarcity of studies assessing patients presenting with the chief complaint of facial papules and face roughness for the diagnosis of FFA or LPP.

Our findings, for the first time, showed that facial papules appear early in the course of the disease, even before the complete presentation of alopecia. The reason for referring patients to the clinic was the roughness of face, and most of the patients had not awareness about concurrent alopecia while they had mild frontotemporalparietal recession.

Previous research showed that 6% to 37% of patients with FFA had concomitant facial papules (13,18,19). According to the largest published series performed retrospectively among 355 cases with the diagnosis of FFA, 14% of patients presented these lesions (15). In the current study, scalp alopecia was observed in all the patients presenting with facial papules, of which 89.7% had FFA. Additionally, five patients were diagnosed with LPP without FFA. Therefore, facial papules could also be an early sign of LPP. Furthermore, the association between LPP and FFA is confirmed by these findings.

FFA is commonly diagnosed in postmenopausal women, while sometimes it occurs in premenopausal women as well as in men (5,6). All our participants were female, and contrary to previous studies, 73.5% of them were premenopausal (15,19,20). The mean age at the onset of the diseases was lower than the previous reports (47.84 years) (15), and the youngest patient was 26-year-old. These findings support the early appearance of facial papules in the course of the FFA and LPP. In addition, facial papules are easily visible at younger ages, but they may disappear over the years, leaving smoother skin without visible follicular orifices (13).

Facial papules are randomly distributed over the facial skin with no desquamation or erythema and decreased or absent vellus. They are more visible over the temporal regions, and inframandibular or retroauricular areas may also be affected (17,21). Histologic examination of these lesions showed vellus hair involvement with a dense follicular lichenoid inflammatory process. Previous studies showed that one-third of patients with FFA might present pruritus and sometimes trichodynia (15). In our study, these symptoms were detected in 38.2% of the patients.

According to previous reports, eyebrow hair loss is developed in 52% to 80% of FFA patients (15,22,23). Similarly, eyebrow involvement was noted in 75% of our cases, while only one of the patients with LPP had eyebrow hair loss. Additionally, body hair and axillary hair involvement were observed in 11.5% (19,20) and 2.9% (15) of the patients, respectively, which are lower than the previous reports, suggesting that they are late presentations of the disease.

Cutaneous and mucosal LP involvements were rare in the FFA patients (8 and 1 patients, respectively). In addition, the association of FFA with LPP at other scalp
locations was frequently observed in our study, while in a previous multicenter report, such an association was rare (15).

Although a genetic effect has not been explained, FFA has been reported more frequently in patients with a positive family history (24). In a recent report of 20 patients, 5% of patients with FFA had a positive family history of the disease (25); however, none of our cases had a family history. Moreover, there are previous reports of the preponderance of nonsmokers in FFA patients (5), whereas none of our patients were smokers, which merits further investigation.

FFA has a T-cell-mediated autoimmune mechanism and is associated with several autoimmune diseases, including hypothyroidism, vitiligo, alopecia areata, rheumatoid arthritis, and lupus (26). In general, 26.5% of our patients had hypothyroidism, similar to what has been previously reported (26). Therefore, it seems that the initial workup of thyroid function should be considered early in the setting of the disease. A history of alopecia areata was also noted in 6 (8.8%) patients. Comorbidities, including dyslipidemia and arterial hypertension (15), were present in 14.7% and 11.9% of the cases, respectively.

Delayed hypersensitivity immune reaction, in which the release of cytokines by activated T cells attracts inflammatory cells and leads to the release of various cytokines and destruction of keratinocytes, plays a role in the pathogenesis of FFA/LPP (27). These chronic inflammatory processes are a component of the metabolic syndrome; thus, they could explain the link between metabolic comorbidities in FFA (27). The greater incidence of hypertension in postmenopausal women may be due to the aging process. We also found coexistence of androgenetic alopecia (AGA) in patients with FFA (25%), while the diagnostic accuracy of AGA varies among different studies (19).

The limitation of our study was the limited sample size; thus, further multicenter studies with larger sample sizes are needed to determine the prevalence of FFA/LPP in patients presenting with facial papules or skin roughness.

In conclusion, this was the first attempt to investigate the diagnosis of FFA and LPP in patients presenting with the chief complaint of facial papules. Our findings showed that facial papules are the silent and early signs of FFA and LPP. Paying attention to these early signs, along with metabolic disturbances, can help with the early diagnosis of FFA and LPP. Interestingly, our patients demonstrated a new variant of LPP. Their unique presentation, involvement, and histopathologic findings call for creating a new disease entity. Our results could be the basis for designing future studies on FFA starting in the premenopausal stage of life.

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Facial papules are early sign of frontal fibrosing alopecia

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