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# Frontal fibrosing alopecia: a cross-sectional study of 108 patients followed at a single center

Ana F. Pedrosa<sup>1,2,3,4</sup>, Ana F. Duarte<sup>1,2,5</sup>, Filipa Ventura<sup>1</sup>, Eckart Haneke<sup>1,6</sup>, Osvaldo Correia<sup>1,2</sup>

- 1. Centro de Dermatologia Epidermis, Instituto CUF, Porto, Portugal;
- 2. Faculty of Medicine, University of Porto, Portugal;
- 3. Department of Dermatology and Venereology, Centro Hospitalar São João EPE, Porto, Portugal;
- 4. CINTESIS Center for Health Technology and Services Research, Porto, Portugal;
- 5. MEDCIDS Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Portugal;
- 6. Department of Dermatology, Inselspital, University of Bern, Bern, Switzerland.

#### Corresponding author:

Ana Filipa Bastos Pedrosa (ORCID 0000-0001-5969-0235)

Centro de Dermatologia Epidermis, Instituto CUF, Porto, Portugal

Rua Fonte das Sete Bicas, 170

E-mail: anabastospedrosa@gmail.com

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#### **Abstract**

**Background:** Frontal fibrosing alopecia (FFA) is a primary scarring alopecia characterized by frontotemporoparietal hairline recession with associated clinical findings crucial for diagnosis and which may be linked to severity and prognosis.

**Objective:** To evaluate clinical-trichoscopic-histological features of a series of FFA cases comparing with published literature.

**Methods:** Clinical, trichoscopic and histological features of FFA cases diagnosed at a single Dermatology Center from 2009 to 2016 were retrospectively reviewed in order to seek for possible correlations. Severity was classified by the largest measure of hairline recession.

**Results:** One-hundred and eight patients were enrolled including 105 females and 3 males with a mean age of 57.8 years. A mild-moderate frontal hairline recession prevailed (53.7%). Premenopausal females represented 26.8% of our sample. Eyebrow loss was depicted in 89.8% being the first noticed sign in 40.7%. Facial papules were observed in 57.4% of patients more commonly found in premenopausal compared with postmenopausal females (P=0.023); they often exhibited histological sebaceous gland hypertrophy. Independent factors for severe FFA include visible frontal veins (OR 4.15; P=0.001), trichoscopic perifollicular erythema and scaling (OR 3.91; P=0.021) and ivory white patches (OR 3.68; P=0.008).

**Conclusions:** Our results support an emergent burden of FFA with an increasing reported prevalence within premenopausal females. Facial papules described as part of the clinical spectrum of FFA were frequently found and especially common among premenopausal females. Trichoscopy represents an important aid in the diagnosis and may herald FFA severity. Treatment is still elusive although antiandrogens, usually combined with topical anti-inflammatory therapies, display a moderate effect. (*J Dermatol Case Rep.* 2017; 11(3): 35-42)

# Background

Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia first described by Kossard in 1994. Since then, an extensive research had emerged on this specific type of alopecia, but its true prevalence, pathogenesis, associated clinical findings, prognosis and treatment still remain unclear. It was regarded as a postmenopausal female

hair disease in the spectrum of lichen planopilaris (LPP) afflicting the frontotemporal and/or frontoparietal region with a symmetric and progressive hairline recession. In fact, and although more common in postmenopausal women, reports of FFA in younger women and even in men are increasing. The coexistence of LPP in other scalp areas or even mucocutaneous lichen planus is considered relatively infrequent. The loss of the eyebrows was recognized as a common and

helpful diagnostic feature, often a presenting isolated sign. Body hair loss is a frequently reported feature, although it may be difficult to distinguish from physiologic changes occurring after menopause. Several attempts have been made in order to classify these patients with respect to the disease severity; even though with some of them being too cumbersome<sup>11</sup> to be used in clinical practice; the most suitable and unanimously acceptable method of categorization has not yet been developed. The aetiology of FFA remains a matter of debate with the most current opinion pointing to a complex interplay between environmental factors and genetic predisposition. Treatment options, often combined, are based mainly on anecdotal reports and still unsatisfactory, resulting in stabilization or eventually discrete improvement.

Trichoscopy represents a valuable tool in this setting supporting the naked eye examination and enabling a rapid and accurate diagnosis, often avoiding the need to perform a biopsy. Scaling and erythema around follicular ostia are the most frequent findings. <sup>16</sup> Histopathology unveils vacuolar interface changes as in LPP. The clinical correlation is crucial for the definite diagnosis, <sup>7</sup> it was with the aid of histopathology that it was possible to group the above mentioned associated clinical features under the same disease process.

# Objective

The aim of this study is to present the results of a series of patients with FFA followed at one Dermatology Center and to review their data concerning demographic, clinical, trichoscopic and histologic features seeking for possible significant correlations. This survey also intends to unveil more details on this still underexplored disease, discussing our findings in the light of the latest available literature.

## Materials and methods

A cross-sectional study was conducted at a Portuguese Dermatology Clinical Center enrolling all patients with FFA observed over a period of 8 years, from January 2009 until December 2016.

Clinical, trichoscopic and, whenever available, histological features of FFA cases were retrospectively reviewed. Demographic and clinical data were collected from the medical databases including patient age, gender, date of diagnosis/ first signs or symptoms, clinical severity (according to the scale developed by Vãnó-Galván et al.3, which included 5 grades: I (1 cm), II (1-2.99 cm), III (3-4.99 cm), IV (5-6.99 cm) and V (>7 cm) with the largest measure of hairline recession being used to establish the patients' grade), associated symptoms (pruritus and/or trichodynia) and clinical findings, such as eyebrow loss, body hair loss, yellow facial papules, visible frontal veins, facial erythema and/or hyperpigmentation. Duration of FFA was stated since the moment the patient referred to see hair or eyebrow loss. The presence and severity of concomitant forms of alopecia, namely androgenetic alopecia (AGA), LPP and alopecia areata were recorded, as well as the evidence of acne, seborrheic dermatitis, vitiligo and mucocutaneous or nail lichen planus. Additional family FFA cases were observed and registered along with any other relevant medical history including the gynecological history for females. Available laboratory blood studies on thyroid function and autoantibodies were analyzed. Treatment strategies employed and their outcome were measured in terms of stabilization, improvement or worsening. For statistical purposes, severity grades were reclassified into mild-moderate (grades I and II) and severe cases (grades III to V).

Trichoscopic digital images were reviewed and classified according to the following on the scalp: perifollicular erythema and scaling, lonely hair, ivory white patches, hair diameter diversity, yellow dots; and on the eyebrows red or gray dots. <sup>16</sup> The technical equipment used for image acquisition was Molemax II® (Derma Instruments, Vienna, Austria) videodermatoscope with a minimum x30 magnification. In many instances a manual dermatoscope, 3Gen DermLite II Pro HR Dermatoscope (San Juan Capistrano, CA, USA), had been used which did not enable a retrospective review of images.

Histopathological features found on the scalp and eyebrows, such as the presence of: a lichenoid perifollicular infiltrate classified in mild, moderate or severe; perifollicular fibrosis (concentric or nonconcentric; superficial and/or deep); and sebaceous gland atrophy were further analyzed by two independent double-blinded pathologists. A similar procedure was applied to the histopathological analysis of the facial yellow papules with the addition of the following criteria: 1) follicular dilatation with keratin plugging; 2) vellus hairs; and 3) sebaceous gland hypertrophy.

Statistical analysis was conducted using IBM SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive frequencies were calculated to characterize the study population. Duration of FFA is reported as the median and range because of the skewed distribution of this variable. The Mann-Whitney U test was used to evaluate the significance of duration of FFA distribution between severity groups. Pearson's chi-squared and Fisher's exact tests were used to compare categorical variables in univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for potential explanatory variables for the severity of FFA using a multivariate logistic regression analysis. *P*-values below 0.05 were considered statistical significant.

# Results

We enrolled 108 patients, 105 women and 3 men, with a mean age of  $57.84\pm12.192$  years (ranging from 29 to 82 years). Table 1 displays demographic, clinical and laboratory findings concerning the female and total patients. From the 3 male patients enrolled (29, 66 and 82 years old), 2 had mild forms (grade I) and loss of eyebrows. Overall we found that a mild-moderate frontal hairline recession predominated (53.7%); we were not able to find a statistically significant difference between the median duration of FFA and a higher severity grade (P=0.376). The majority of patients (89.8%, 97/108) had eyebrow involvement (Fig. 1), which

was the first noticed sign in 44 patients and the isolate finding, so far, in 2 patients. Facial papules were present in 57.4% (62/108); located on the periocular area, chin, cheeks or diffusely distributed throughout the face (Fig. 2). Premenopausal females exhibited more commonly these papules compared with postmenopausal ones (P=0.023). Although papules were more frequently depicted in severe cases yielding 55.9% compared with 44.1% in mild-moderate forms, the difference was not statistically significant (P=0.611),

neither in premenopausal nor in postmenopausal females. Frontal veins were visible in more than half of the patients (58.3%) previously to the application of topical steroids, either depressed (44.4%) or protruding on palpation (13.9%) and their presence was significantly associated with severe FFA in univariate analysis (P=0.002). From the analyzed clinical variables (Table 1), visible frontal veins were the single independent factor associated with severe FFA (OR 4.15; 95% CI 1.74-9.89; P=0.001) after adjusting for potential

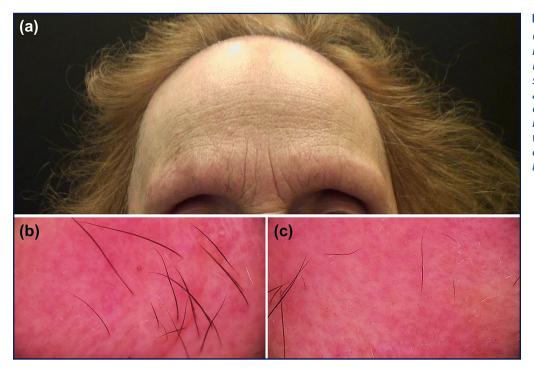


Figure 1
Clinical and trichoscopic features of eyebrow involvement in FFA. (a) Frontal hairline recession and eyebrow loss reported as first event. (b) Eyebrow trichoscopy showing sparse hairs surrounded by erythema without scale. (c) Eyebrow trichoscopy with red dots regularly distributed over the field.

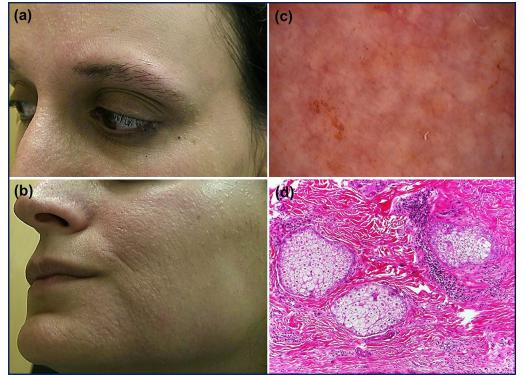


Figure 2

Clinical-dermatoscopic and histological appearance of facial papules. (a) and (b) Facial papules diffusely distributed throughout the face conferring a roughness texture. (c) Dermatoscopy unveiling large light-yellow dots regularly distributed with no vellus hairs. (d) Hypertrophic sebaceous glands associated with a mild inflammatory mononuclear infiltrate, without hair follicles (HE, x200).

**Table 1**Demographic, clinical and laboratory results according to menopausal status, total number of females and total number of patients.

	FEMALES			T. 15 % .
	Premenopausal	Postmenopausal	Total	Total Patients
Patients; n (%)	29 (26.8)	76 (70.4)	105 (97.2)	108 (100)
Age in years; mean (range)	43.74 (30-55)	63.16 (49-84)	57.81 (30-84)	57.84 (29-84)
Duration in months; median (range)	0 (0-120)	12 (0-180)	12 (0-180)	12 (0-180)
Severity grade; median	II	III	III	III
Loss of eyebrows; n (%)	26 (89.7)	69 (90.8)	95 (90.5)	97 (89.8)
Loss of eyebrows as first sign; n (%)	17 (58.6)	26 (34.2)	43 (40.9)	44 (40.7)
Occipital hair loss; n (%)	1 (3.4)	11 (14.5)	12 (11.4)	13 (12.0)
Body hair loss; n (%)	9 (31.0)	8 (10.5)	17 (16.2)	18 (16.7)
Facial papules; n (%)	22 (75.9)	39 (51.3)	61 (58.1)	62 (57.4)
Visible frontal veins; n (%)	17 (58.6)	46 (60.6)	63 (60.0)	63 (58.3)
Facial erythema; n (%)	3 (10.3)	15 (19.7)	18 (17.1)	19 (17.6)
Hyperpigmentation; n (%)	20 (69.0)	68 (89.5)	88 (83.8)	90 (83.3)
Pruritus and/or trichodynia; n (%)	0	3 (3.9)	3 (2.9)	3 (2.7)
Androgenetic alopecia; n (%)	6 (20.6)	27 (35.6)	33 (31.4)	34 (31.5)
Lichen planopilaris; n (%)	4 (13.8)	11 (14.5)	15 (14.3)	16 (14.8)
Alopecia areata; n (%)	0	2 (2.6)	2 (1.9)	2 (1.9)
Vitiligo; n (%)	0	4 (5.3)	4 (3.8)	4 (3.7)
Mucocutaneous lichen planus; n (%)	1 (3.4)	3 (3.9)	4 (3.8)	6 (5.6)
Acne; n (%)	1 (3.4)	1 (1.3)	2 (1.9)	2 (1.9)
Seborrheic dermatitis; n (%)	7 (24.1)	10 (13.2)	17 (16.2)	19 (17.6)
Family history; n (%)	4 (13.8)	8 (10.5)	12 (11.4)	12 (11.1)
Hypothyroidism; n (%)	2 (6.9)	15 (19.7)	17 (16.2)	17 (15.7)
Antithyroid antibodies; n (%)	6 (20.7)	10 (13.2)	16 (15.2)	16 (14.8)
Antinuclear antibodies; n (%)	2 (6.9)	8 (10.5)	10 (9.5)	10 (9.3)

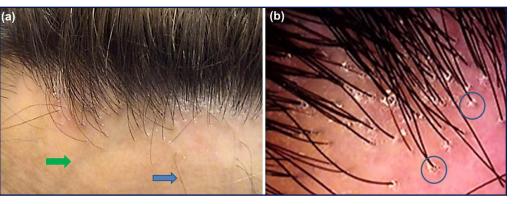


Figure 3

Clinical and trichoscopic features of FFA. (a) Recession of frontal hairline with clinically apparent scales, depression of the frontal veins (green arrow) and lonely hair (blue arrow). (b) Trichoscopy revealing scaling and slight erythema increase around hair follicles (blue circles).

confounding variables such as menopausal status, eyebrow involvement and facial papules.

Androgenetic alopecia was the most frequently associated alopecia co-occurring in 31.5% (34/108), followed by LPP in 14.8% (16/108). A family history of FFA was recorded in 11.1% (12/108).

Scalp digital trichoscopy was performed in 91.9% (91/99)

and unveiled, most frequently, lonely hair (90.1%, 82/91) followed by perifollicular erythema plus scaling (76.9%, 70/91) as seen in Fig. 3, and ivory white patches (57.1%, 52/91). Figure 4 shows a coexistence of FFA (with occipital involvement) and LPP in the same patient and FFA frontal hairline trichoscopy. On univariate analysis, we found that perifollicular erythema and scaling were significantly asso-

ciated with severe FFA (P=0.014), as were ivory white patches (P=0.002). On multivariate logistic regression analysis, the aforementioned variables with statistical significance on chi-squared test adjusted for menopausal status were independently associated with FFA severity: perifollicular erythema and scaling (OR 3.91; 95% CI 1.23-12.44; P=0.021) and ivory white patches (OR 3.68; 95% CI 1.41-9.59; P=0.008).

Eyebrow digital trichoscopy performed in 36.1% (39/108) revealed red dots (Fig. 1) in 20 and grey dots in 8 cases. We could not find a statistically significant association between these dots and the severity of FFA.

Scalp and/or eyebrow biopsied cases (49.1%, 53/108) showed a lichenoid lymphocytic infiltrate (Fig. 5), with se-

baceous gland atrophy in 90.5% (48/53) and perifollicular fibrosis in 84.9% (45/53). Facial papules were biopsied in 29.0% (18/62) revealing a lichenoid lymphocytic infiltrate with perifollicular fibrosis in 55.6% (10/18) and follicular plugging in 27.8% (5/18). In more than half of the biopsied yellow facial papules (55.6%, 10/18), we found a pronounced sebaceous gland hypertrophy without vellus hair follicles.

Most of our patients (73.1%, 79/108) were under combined intralesional and topical treatments, namely intralesional steroids (triamcinolone acetonide 40 mg/ml) diluted 1:2 in the frontal region and 1:3 in eyebrows and injected every 8 weeks until suppression of the inflammation, plus topical minoxidil 5% solution and pimecrolimus in cream, both once daily.

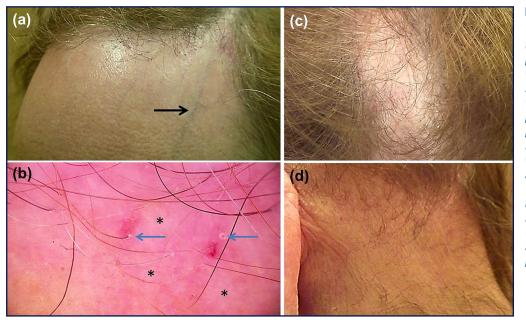


Figure 4

Coexistence of FFA and LPP in the same patient. (a) Frontotemporal hair recession associated with roughness on palpation. Visible frontal veins (black arrow) with a slight depression on palpation and skin atrophy (without previous application of topical steroids). (b) Trichoscopy showing perifollicular erythema and a discrete scale (blue arrows) involving the sparse hair follicles in a milky red background interspersed with ivory white patches (asterisks). (c) Parieto-occipital alopecic patch of LPP. (d) Occipital involvement of FFA.

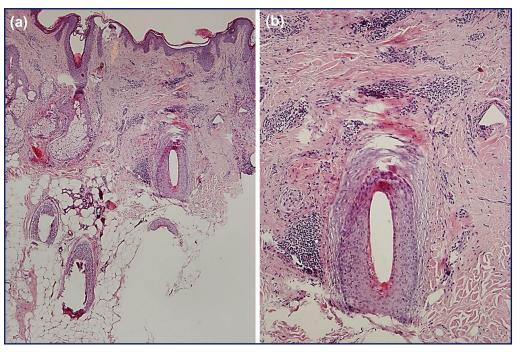


Figure 5
Histological features of FFA. (a)
Sparse hair follicles displaying
thinning of the follicular epithelium with a mild perifollicular lichenoid inflammatory infiltrate
(HE, x40). (b) Higher magnification (HE, x200) shows the vacuolar degeneration of the follicular keratinocytes and con-

centric perifollicular fibrosis.

Among patients under oral treatments (40.7%, 44/108), finasteride 2.5-5 mg/day was the most common option in females (n=29; noting that 14 patients had concomitant AGA) followed by spironolactone 25-50 mg/day (n=11), often combined with topical treatments and adequate iron and vitamin supplements, resulting in discrete improvement or stabilization of FFA in a median follow-up period of 31 months (range 4-96 months).

### **Discussion**

Despite the efforts towards a better understanding of this relatively recently recognized disease, there are still many issues to explore. Therefore, case series of patients represent a valuable contribution to a better understanding of FFA. Our results, coming from one of the biggest case series of patients from a single private Dermatology Center described in the literature, support a high prevalence of FFA being increasingly detected among premenopausal women. We acknowledge that it may be related to our better and keen clinical (and trichoscopy) acumen to this particular form of primary cicatricial alopecia.

In contrast with other authors,<sup>3</sup> we did not find a correlation of the duration and the severity grade of FFA, which may be due to a spontaneous stabilization already described in the natural history of this disease. There is a need to mention that duration of FFA may be a biased measure since the patients might not accurately remember the beginning of the alopecia.

The majority of our patients were females and the number of male patients is too small to have an impact on the results. The increasingly reported premenopausal women cases<sup>3</sup> are in accordance to what we have found (26.8% of premenopausal women; the youngest was 30 years old) and should alert the clinician to search for FFA stigmas on frontotemporal hairline, eyebrows, occipital area and facial skin to promptly institute treatment in earlier stages.

Worthwhile to notice is the high frequency of yellow facial papules detected in our study (57.4%) which considerably surpassed the number found in other series (6, 14, 20 and 37%). The statistically significant higher frequency of facial papules in premenopausal females may herald a precocious disease phase<sup>17</sup> which should alert the clinician for FFA diagnosis. In contrast with other authors,<sup>3</sup> the presence of facial papules in our study was not associated with severe FFA. Conversely, visible frontal veins were significantly associated with severe FFA resulting from marked skin atrophy of the forehead, presumably due to scarring.<sup>20</sup>

We found 12 cases (11.1%) displaying a history consistent with familial FFA (confirmed by the dermatologist) which was also reported in other series, but herein with a tendency for increasingly detected familial cases supporting the importance to search for it in the personal history and highlighting the need to seek for a genetic unexplored component.<sup>23</sup>

The prevalence of hypothyroidism (15.7%) was similar to the one reported by other authors supporting the need to include thyroid function analysis in the initial laboratory panel of

FFA. Curiously and with the possible exception of antithyroid antibodies found in 14.8% of cases, our results do not support a robust association with autoimmunity as the number of patients with vitiligo, alopecia areata and antinuclear antibodies were almost negligible (Table 1) in accordance to the report by Vãnó-Galván et al.<sup>3</sup>. Sixteen patients (14.8%) had evidence of coexistent LPP afflicting non-marginal scalp (considered by some authors a hair-specific autoimmune disorder<sup>24</sup>), a similar prevalence to the one reported by Samrao et al.<sup>25</sup>, although more recent series had found this association infrequently emphasizing FFA as a clinically distinct entity.

Trichoscopy was performed in almost all of our patients and commonly unveiled erythema and discrete scaling involving the remaining hair follicles, which aided in the diagnosis and monitoring of disease activity. Some authors postulated that perifollicular erythema may persist without progression in hairline recession, therefore not always being an indicator of active inflammation and presumably representing histological atrophy or vascular changes.<sup>28</sup> In contrast to the findings of Fernandez-Crehuet et al.,<sup>27</sup> our results demonstrated that perifollicular erythema and scaling were independently associated with severe FFA in multivariate analysis. Ivory white patches, characteristically linked to scarring and atrophy, were significantly associated with severe FFA as previously reported,<sup>27</sup> even when adjusting for perifollicular erythema and scaling and menopausal status. The improved diagnostic accuracy given by the clinical and trichoscopic examinations yielded less biopsy specimens and, therefore, we did not have enough histological slides to establish a strict correlation with disease inflammatory activity.

We did not find a higher prevalence of AGA among FFA female patients compared to the prevalence of AGA in the general population;<sup>29</sup> more than half of FFA patients under oral finasteride did not exhibit concomitant AGA (51.7%, 15/29), reinforcing that the outcome of oral finasteride in our cases was not solely related with an improvement of AGA and an increase in hair density at frontal hairline as other authors claimed.<sup>30</sup> In fact, we do not have patients who were exclusively under oral finasteride to conclude on its true intrinsic value. Due to the retrospective nature of this study and given that the available therapeutic options are so sparse and based on case reports and case series, it did not seem reasonable to use single drugs or formulations to manage this so distressing and cosmetically embarrassing disease.

Nevertheless, the therapeutic effect of finasteride in FFA remains elusive, as well as its mechanism of action in this setting, given that a hormonal pathogenesis had never been proved with studies unveiling normal laboratory sex hormone analysis.<sup>5</sup> Furthermore, a recent study by Ranasinghe *et al.*<sup>31</sup> showed an androgen deficiency in FFA. From another point of view, there are reports of an intrinsic anti-inflammatory action of finasteride in other settings, namely in chronic bacterial prostatitis where this drug evidenced a significant *in vitro* reduction of the inflammatory cell infiltration.<sup>32</sup>

Other therapeutic options including topical calcineurin inhibitors were frequently added to reduce the inflammatory process when applied to the frontal hairline and eyebrows. In our cases we have used mainly pimecrolimus cream due to its preferred cosmeticity over tacrolimus ointment.

Although it was not a main objective of this study given the retrospective nature, we sought to describe the treatment used and the overall response. Due to the absence of guidelines or unanimously efficacious treatment options, we found a great variability in drugs used which were often combined including topical, intralesional and systemic therapies. Thus, this study does not enable to evaluate the efficacy of the different reported therapeutic options properly. Nevertheless, it may pave the way to future prospective surveys to compare the efficacy of different treatment modalities in this setting.

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