Case Report

Primary cutaneous follicle center lymphoma presenting as frontal fibrosing alopecia

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Abstract

Primary cutaneous follicle center lymphoma rarely presents as macular alopecia and is typically characterized by solitary papules and nodules on the head, neck, and trunk. We report a 24-year-old woman with frontal alopecia that clinically resembled frontal fibrosing alopecia but was ultimately diagnosed as primary cutaneous follicle center lymphoma. The patient presented with pronounced alopecia over the left frontal scalp superimposed on milder bitemporal alopecia and intermittent symptoms of scalp irritation. Histopathologic examination of a scalp biopsy revealed a nodular lymphocytic infiltrate with irregular germinal centers localized to the adventitial dermis of the eccrine coil and the interadnexal interstitium. Immunophenotyping confirmed B-cell clonality, with findings consistent with primary cutaneous follicle center lymphoma. This case highlights the importance of biopsy in atypical alopecia presentations, as histologic findings were pivotal in diagnosing primary cutaneous follicle center lymphoma with concurrent frontal fibrosing alopecia features.

Introduction

Causes of frontal alopecia typically include traction alopecia, frontal fibrosing alopecia (FFA), androgenetic alopecia, and rare cases of alopecia areata falling under the designation of alopecia areata incognito.[1] A neoplastic process would not typically be a primary consideration. We report an unusual presentation of primary cutaneous follicle center lymphoma (PCFCL), characterized by frontal alopecia that was clinically most consistent with FFA. PCFCL is a low-grade B-cell lymphoma, typically presenting with solitary or regionally distributed papules and nodules most frequently located in the head, neck, and trunk areas.[2] Although it is most seen in middle-aged white men, this lymphoma also occurs in women, and all age ranges can be affected, including its occurrence in the pediatric setting in children and adolescents. The prognosis is excellent, and the usual treatment is excision or radiation when patients present with localized disease; more extensive cutaneous disease could necessitate therapy with a single agent drug like rituximab.[2] The multidrug regimen that would be used to treat the nodal counterpart would be reserved for rare cases that have a more aggressive clinical course.[2] The clinical and light microscopic findings along with molecular studies of the current case are presented and the literature is reviewed as it pertains to macular alopecia as the defining presentation in the setting of PCFCL.

Case Synopsis

A 24-year-old woman with a four-year history of hair loss, primarily involving the hairline, presented with a localized patch of pronounced alopecia on the left frontal scalp (**Figure 1A**). However, it was superimposed on a background of milder bitemporal alopecia that was most reminiscent of FFA (**Figures 1B-C**). Two years prior, the affected areas developed intermittent irritation, flaking, itching, and transient bumps that spontaneously resolved within approximately one month. She denied any other areas of hair loss or red, scaly patches and did not treat these lesions with medication. She had previously used topical minoxidil to manage her hair loss, which she tolerated well, though without improvement. Although she presented with her hair worn naturally, she had previously worn unspecified tighter hairstyles. The patient had a family history of cicatricial alopecia; her mother experienced similar patchy hair loss with erythematous bumps scattered throughout the scalp. There

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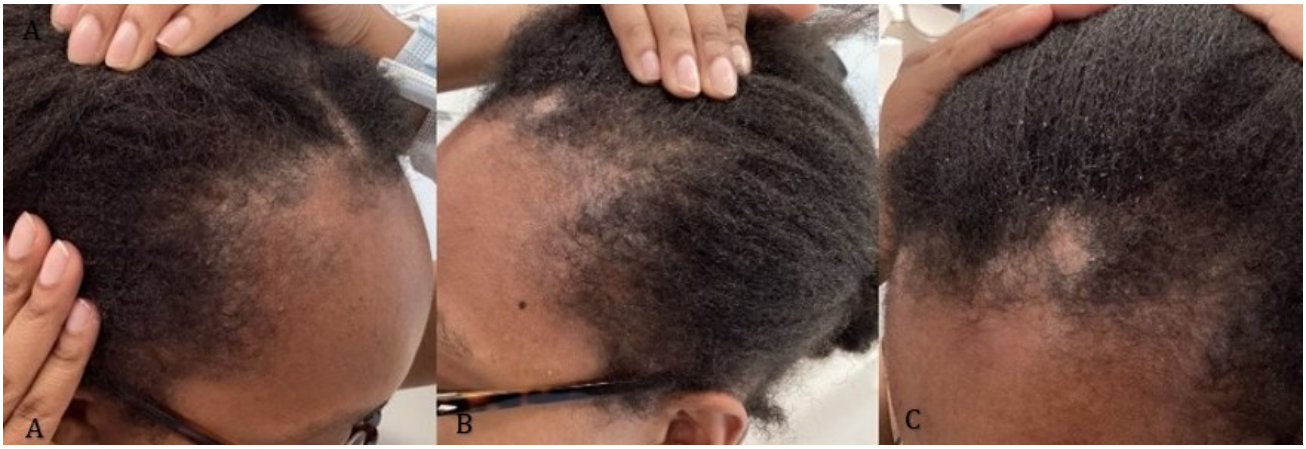

Figure 1. ***A-B)*** *This 24-year-old woman presented with generalized and moderate hair loss on the scalp accentuated in the temporal areas bilaterally.* ***C)*** *However, there was a noticeable patch of more striking alopecia in the left temporal area, which prompted the biopsy for further evaluation.*

was no known family history of cancer or other autoimmune conditions.

Upon physical examination, there were patches of hair loss consistent with alopecia, without any erythema or underlying scalp lesions observed. The clinical differential diagnoses included traction alopecia, FFA, and androgenetic alopecia, recognizing that the unilateral distribution of the alopecia was very unusual. She was prescribed topical minoxidil 10% and 0.05% betamethasone twice a day. When she returned two weeks later for further evaluation and management, a punch biopsy of her left superior medial forehead was performed.

The horizontally sectioned scalp biopsy revealed a striking nodular lymphocytic infiltrate in the lower isthmic region of the hair follicle and around the eccrine coil (**Figure 2A**). This infiltrate had irregular, variably sized germinal center foci that had a distinct proclivity for the adventitial dermis of the eccrine coil, although there was some degree of infiltration of the interadnexal interstitium (**Figure 2B**). The germinal centers were not surrounded by a mantle zone equivalent to small lymphocytes nor was there polarization of the germinal centers. In addition, there was a predominance of small centrocytic cells, many of which had a spindled elongate appearance and were without any admixed tingible body macrophages (**Figure 2C**). In the proximal sections where the dermal epidermal junction was visualized, there was a focal folliculocentric lymphocytic infiltrate with associated thinning of the outer root sheath epithelium and with supervening folliculocentric elastolysis and fibrosis (**Figure 2D**).

Comprehensive phenotypic studies were performed. *CD3* staining showed T-cells in the interadnexal interstitium (**Figure 3A**), as well as surrounding and permeating germinal center foci (**Figure 3B**). In the distal portion of the horizontally sectioned scalp sample, *CD20* highlighted B-cells, which were concentrated in atypical germinal center foci whereby the T- to B-cell ratio was likely 1:1 (**Figure 3C**). Proximal sections had a dominant T-cell infiltrate with minimal B-cells (**Figure 3D**). *CD10* and *BCL6* highlighted germinal center foci, with significant *CD10* expression among centrocytes and centroblasts (**Figure 3E-F**). Both markers demonstrated the irregular infiltrative quality of the nests. In addition, the *Ki67* proliferation was less than the very high index seen in a normal germinal center. *CD21* and *CD23* highlighted a dendritic cell network but there were significant foci of dendritic cell lysis (**Figure 3G**). *BCL2* showed a strong pattern of immunoreactivity in follicular helper T-cells; however, there was a distinct pattern of cytoplasmic immunoreactivity in a minor subset of lymphocytes with centrocytic or centroblastic morphology (**Figure 3H**). Kappa and lambda studies showed a normal ratio amidst the rare plasma cells present. The spirochete antibody preparation was negative. The combined light microscopic findings and phenotypic profile were held to be diagnostic of PCFCL with possible concurrent features of FFA.

A subsequent skin biopsy, this time from the right superior medial forehead, revealed an atypical B-cell infiltrate within a background of reactive T-cell hyperplasia. These findings represented a morphologic continuum of the previously diagnosed PCFCL. Molecular studies were conducted, and results were negative for a lymphoid gene panel, including *BCL2*. The patient was referred to a cutaneous lymphoma expert for further management.

Discussion

PCFCL presenting as macular alopecia mimicking FFA is an exceptionally rare presentation that underscores the potentially heterogeneous clinical features of this lymphoproliferative disorder. It also emphasizes the importance of performing scalp biopsies on patients with alopecia, particularly when the clinical presentation is atypical as in this case in which the quality and distribution of alopecia suggested FFA, yet the appearance of a localized patch of pronounced alopecia was clearly unusual. This presentation is perplexing when the typical clinical features of PCFCL are not seen.

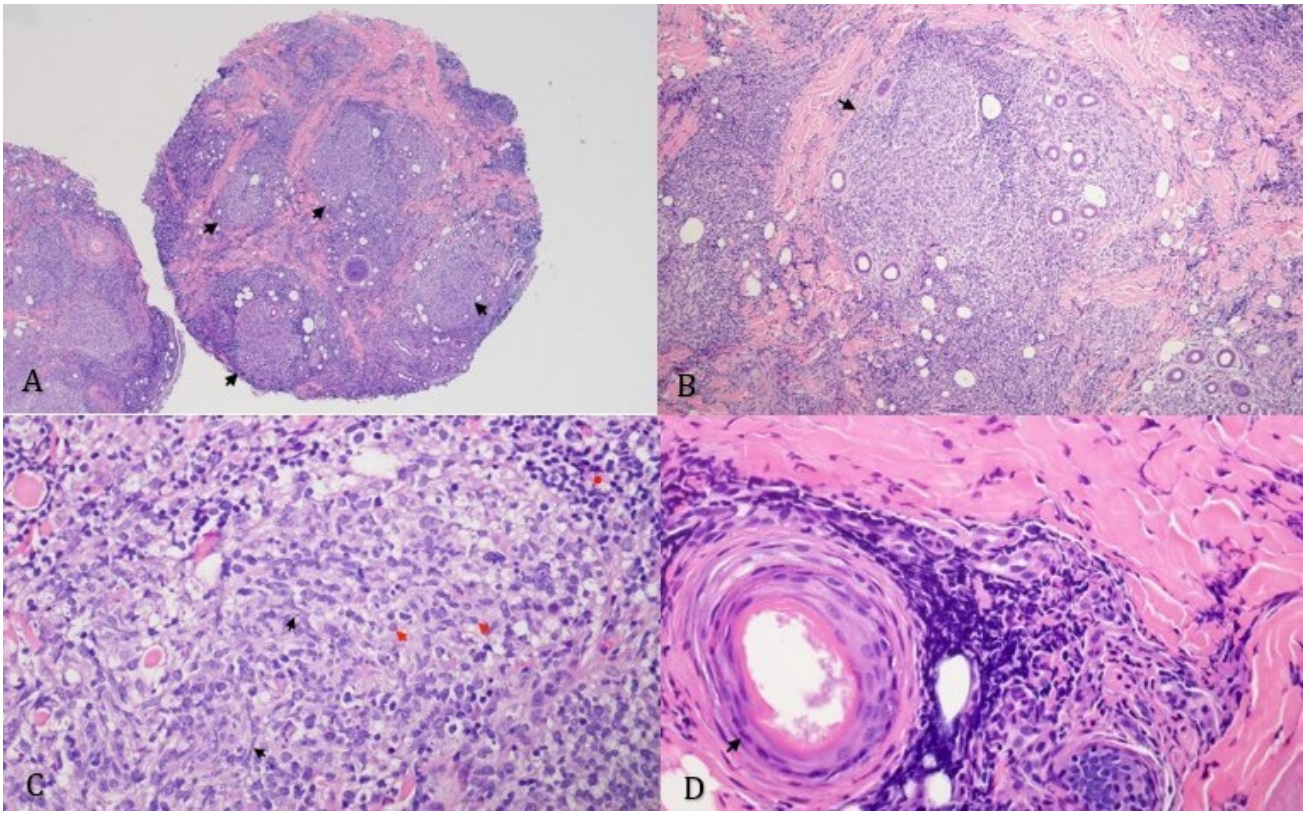

Figure 2. ***A)*** *The horizontally sectioned scalp biopsy exhibited a significant reduction in hair follicle density in association with a striking nodular lymphocytic infiltrate (black arrows) at the level of the eccrine coil (x4).* ***B)*** *In the more distal areas of the scalp biopsy, unpolarized, irregular, variably sized germinal centers (black arrow) were observed. They had a close association with the eccrine coil and focally assumed an infiltrative growth pattern (x10).* ***C)*** *The germinal center foci, while showing a mixture of centrocytes and centroblasts, exhibited a predominance of centrocytes (red arrows) and a number of the follicle center cells had an elongate dendritic appearance (black arrows) (x40).* ***D)*** *In the proximal sections, a folliculocentric small nongerminal center lymphocytic infiltrate was observed. There was concurrent thinning of the outer root sheath epithelium (black arrow) along with perifollicular fibrosis (x40).*

The key in making the diagnosis in this case is the patient's biopsy. Although there was some evidence of a scarring alopecia in the proximal section of the horizontally sectioned scalp biopsy, the more impressive and dominant morphology was the impressive deeper-seated atypical B-cell hyperplasia, highlighted by extensive CD20 positivity in germinal center foci. The diagnosis of PCFCL was based on certain light microscopic findings, namely presence of unpolarized germinal centers, absence of the typical heterogeneous mixture of centrocytic, centroblastic, small lymphocytes and macrophages, and an infiltrative growth pattern replacing the adventitial dermis of the eccrine coil.[2] The phenotypic profile also supported a diagnosis of PCFCL given the lower-than-normal *Ki67* proliferation index, the disruption of the dendritic cell network outlined by the follicular dendritic cell markers *CD21* and *CD23*, and the aberrant BCL2 profile, which exhibited variable *BCL2* expressions amidst some of the centrocytic and centroblastic elements.[2] Although the positive staining of atypical centrocytes and centroblasts for *CD10*, *BCL6*, and *BCL2* mirrors the phenotypic profile in primary nodal follicular lymphoma, the variable staining pattern for *BCL2* ranging from positive to negative within the follicle center cell population is a cardinal hallmark of PCFCL.[2]

Massone et al reported nine patients who presented with hypochromic ill-defined erythematous macules on the scalp associated with hair loss (**Table 1**).[3] These patients, males and females ranging from 44 to 71 years of age, were clinically never thought to have follicle center lymphoma; the diagnosis was established based on histologic examination of scalp biopsies.[3] There are other reports of alopecia in the setting of PCFCL, but these cases describe infiltrative annular plaques and nodules defining a classic presentation of PCFCL but with superimposed alopecia.[4-8] An important feature in this case was the presence of a folliculocentric benign T-cell infiltrate with associated thinning of the follicular epithelium and perifollicular fibrosis, essentially defining a constellation of findings compatible with FFA. The initial event may have been PCFCL development, followed by a collapse in hair follicle immune privilege. Normally, hair follicles are sites of immune privilege, in which downregulation of major histocompatibility complex class I and II prevent immune cell infiltration.[9] Autoimmune alopecia results from a disruption to this immune privilege, though the exact trigger of this disruption remains unknown.[9] An al-

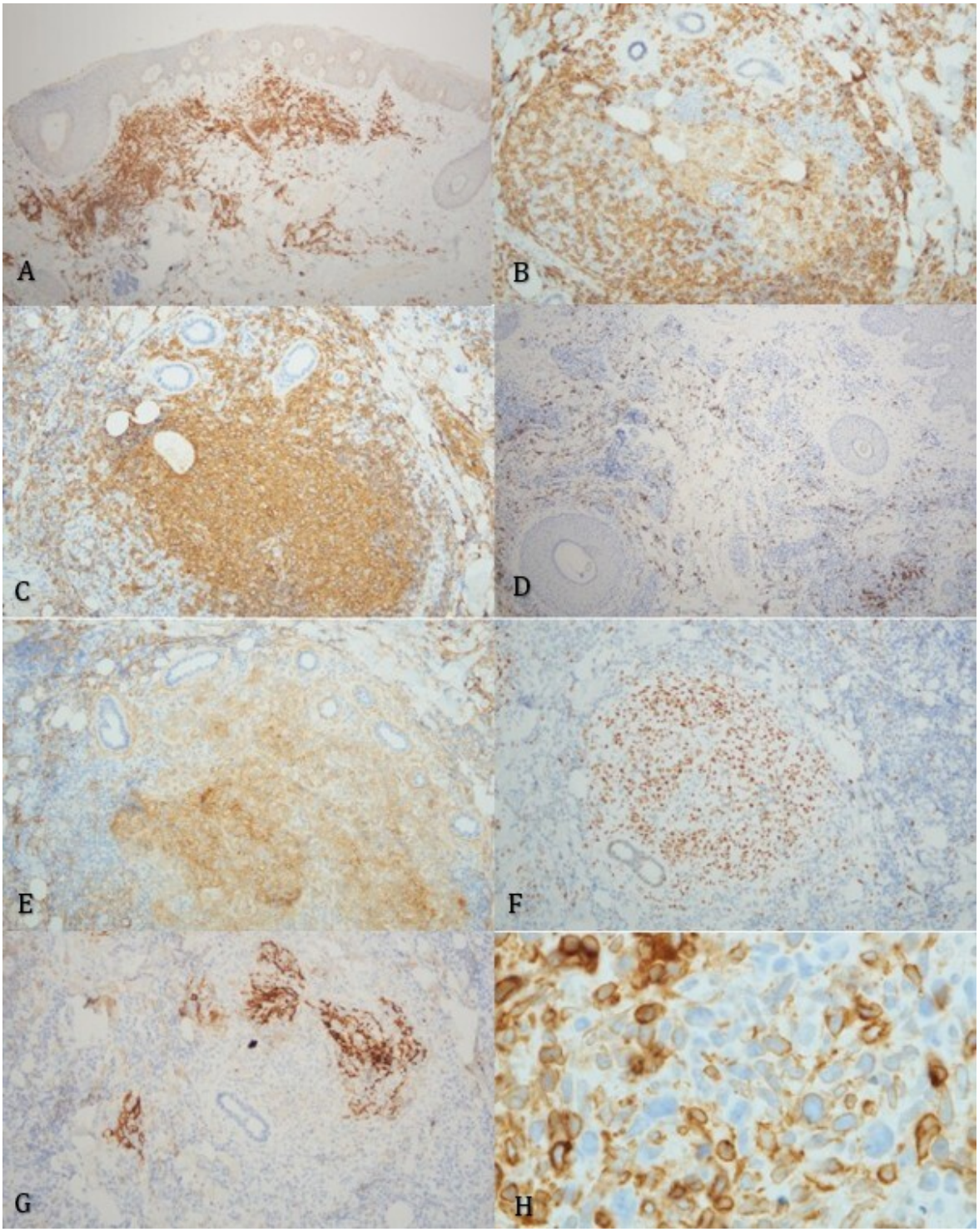

Figure 3. ***A)*** *The* CD3 *stain highlighted T-cells in the interadnexal interstitium (x10,* CD3*) and* ***B)*** *T-cells surrounded and permeated the germinal center foci (x20,* CD3*).* ***C****) In contrast, the* CD20 *stain demonstrated the striking degree of B-cell infiltration whereby the B-cells were localized to the atypical germinal center foci (x20,* CD20*).* ***D)*** *In the proximal portion of the horizontally sectioned scalp sample, the* CD20 *stain demonstrated a minimal B-cell component (x20,* CD20*).* ***E)*** *In the deeper dermis, the atypical germinal center foci became visible and were highlighted by the* CD10 *staining pattern in centrocytes and centroblasts within the atypical germinal center foci (x20,* CD10*).* ***F)*** *The* BCL6 *stain demonstrated strong nuclear staining of centrocytic and centroblastic cells within the atypical perieccrine germinal center focus (x20,* BCL6*).* ***G)*** CD21 *stain highlighted the dendritic cell network within the atypical germinal center foci whereby there was irregularity in the network with focal areas of dendritic cell disruption (x20,* CD21*).* ***H)*** *The* BCL2 *stain showed a strong pattern of immunoreactivity in follicular helper T-cells and a variable staining pattern in the neoplastic centrocytes and centroblasts ranging from positive to negative (x20,* BCL2*).*

Table 1. *PCFCL on the Head Presentation With Macular Alopecia.*

Cases	Age/ sex	Clinical presentation	Scarring
Current case Case report	24/F	Localized unilateral patch of significant alopecia on the left frontal scalp superimposed on a background of milder bitemporal alopecia	Yes
Massone et al,[6] 2016 Case series	67/F	Ill-defined, partly hypopigmented, partly erythematous macule with telangiectasia on the forehead and both parietal regions and subtle scarring alopecia on the vertex	Yes
	47/F	Small area of scarring alopecia on the vertex	Yes
	57/M	Diffuse erythematous macule on the forehead and both parietal regions	No
	44/M	Diffuse erythematous macule on both parietal regions	No
	70 M	Ill-defined erythematous macule on the forehead	No
	54/M	Diffuse, ill-defined erythematous macule on the parieto-occipital region	No
	56/F	Diffuse erythematous macule on the forehead and both parietal regions	No
	71/F	Clinically inconspicuous lesion extending on both parietal regions	No
	64/M	Ill-defined erythematous, partly hypopigmented macules on the forehead and both parietal regions	No

Abbreviations: F, female; M, male.

teration in the follicular T-cell microenvironment attributable to the concurrent adjacent lymphoma may explain the immune privilege collapse.

Conclusion

This case of PCFCL presenting as macular alopecia mimicking frontal fibrosing alopecia illustrates the complex clinical spectrum of PCFCL. Although FFA and other common forms of alopecia are more typically considered in cases of frontal hair loss, this report emphasizes the importance of maintaining a broader differential diagnosis. A thorough histopathologic and immunophenotypic evaluation was critical in reaching the diagnosis, revealing a deeper-seated atypical B-cell proliferation against a background of FFA. Further studies exploring the relationship between lymphomas like PCFCL and alopecia are warranted to better understand potential mechanisms and guide diagnostic approaches.

Potential conflicts of interest

The authors declare no conflicts of interest.

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