Alopecia Areata preceding Mycosis Fungoides

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Citation

R Creed, J Vu, R Singh, D Jones, M Duvic. *Alopecia Areata preceding Mycosis Fungoides*. The Internet Journal of Dermatology. 2006 Volume 5 Number 2.

Abstract

We present two patients presenting with alopecia areata of hair bearing areas for several years before the diagnosis of mycosis fungoides. The overlap between these disorders is discussed.

Funding Sources: The Sherry Anderson Patient Research Fund, The National Alopecia Areata Registry

Conflict of Interest Disclosure: Dr. Duvic is PI of the NIAMS scheduled Alopecia Areata Registry

CASE 1

A 42-year-old white male self-referred himself to the Alopecia Areata Registry. He related a 3 year history of pruritus over well-defined patches of hair loss without epidermal changes on the arms, legs, back, and chest. Alopecia areata (AA) was diagnosed one year prior to presentation and did not improve with topical triamcinolone applied twice a day for a month. On physical exam, a single lichenified plaque was present on the right lower leg [Figure 1A]. Large oval patches of hair loss without inflammation or follicular prominence were present on the anterior and posterior thighs, lower and mid abdomen, back, upper buttocks, forearms, and beard area and covered 19% of his body surface area (BSA). Scalp and nails were normal. Grouped 2-3 mm follicular papules in clusters were present on his upper arms and posterior neck and were less than 1% BSA. Several well-demarcated, oval-shaped pink patches with alopecia were present on the upper back [Figure 1B]. Acne folliculitis was also noted on the buttocks and right inner thigh, and culture grew enterococcus.

Figure 1

Figure 1a (Clinical lesions in case 1): Patches of alopecia on bilateral legs with a single lichenified plaque. Biopsy showed a ruptured cyst with overlying lichenification and a scant atypical T-cell infiltrate with folliculotropism.

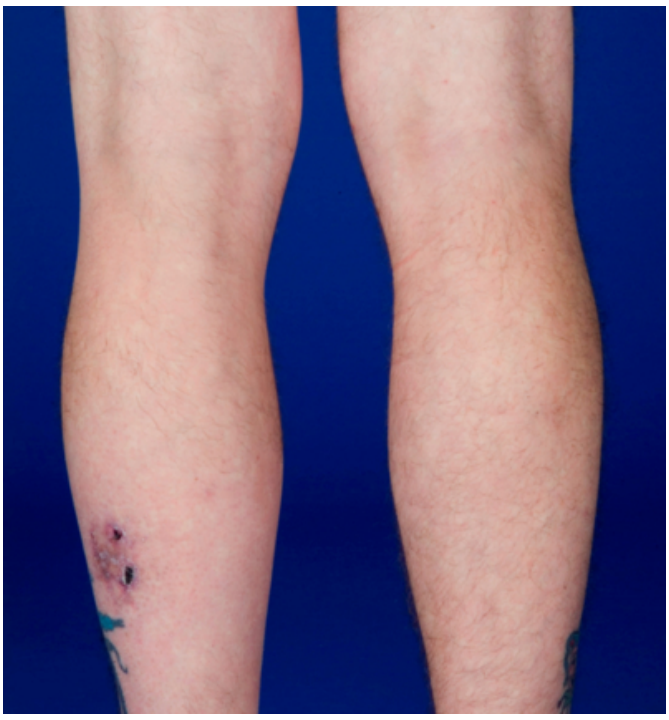
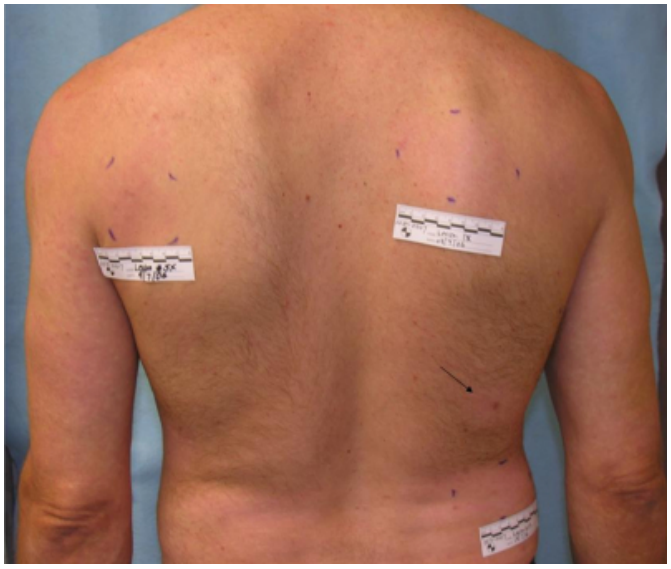


Figure 2

Figure 1b: (Clinical lesions in case 1): Case 1's back with large, oval patches of alopecia and pink oval patches of alopecia. Arrow indicates biopsy site at the center.



Lesions skin biopsy specimens from the plaque [Figure 1A] showed a ruptured epidermal cyst with a lymphocytic infiltrate. The histology of the oval pink patch with alopecia on the back [Figure 1B, arrow] showed a scant infiltrate of small atypical CD4+ T-cells surrounding dermal blood vessels and hair follicles without mucin [Figure 2]. Biopsy specimen taken from a follicular papule of the neck was diagnostic of folliculotropic MF. Identical monoclonal T-cell receptor V gamma-I chain gene rearrangements were detected by a multicolor PCR amplification assay from the different skin lesions. Staging workup including flow cytometry of the blood was negative. Folliculocentric mycosis fungoides (MF), stage IB was diagnosed, and the patient was started on 10% topical mustargen.

Figure 3

Figure 2a: (Histology of Lesion from back of Case 1)Atypical T-cell lymphoid infiltrates surrounding dermal blood vessels and hair follicles without mucin (20X).

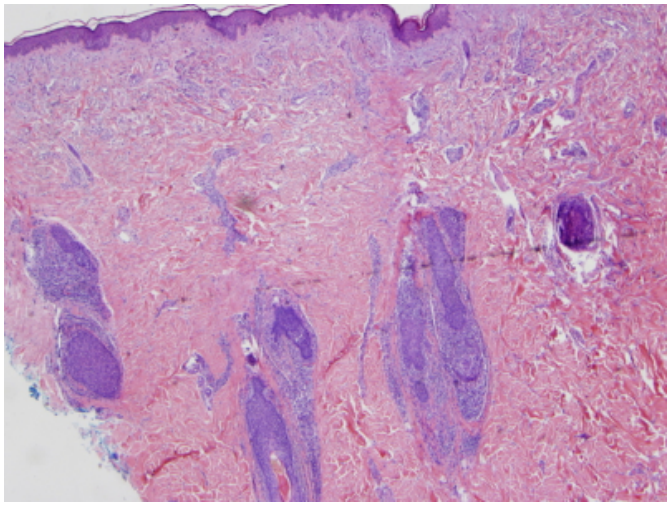
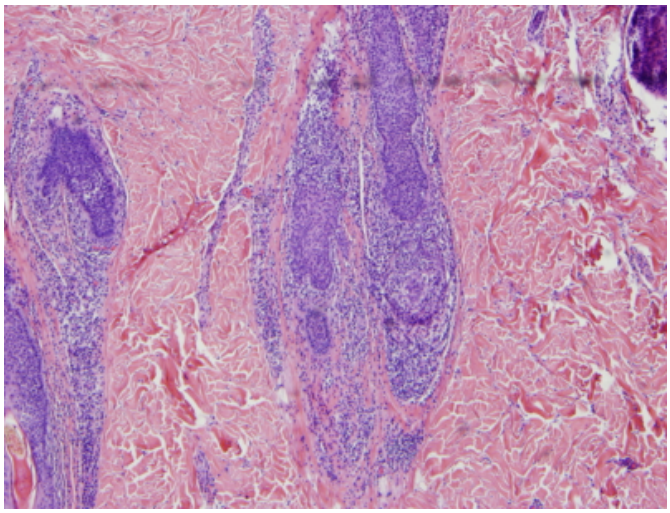


Figure 4

Figure 2b: (Histology of Lesion from back of Case 1) Higher magnification showing perifollicular infiltrates (40X).



CASE 2

A 20 year old healthy male had a two year history of an enlarging patch of hair loss on the posterior leg. He subsequently noted mild scaling and developed new smaller patches of hairloss on the other leg and abdomen. There was no improvement with topical clobetasol or imiquimod. On later exam patches of hair loss and other pink patches covered 10% of the body. Folliculitis was also noted, and skin culture grew staphylococcus aureus. Histology of biopsy from a patch showed an atypical dermal lymphoid infiltrate with epidermotropism. Cells stained positive for

CD3 and CD8. There was loss of CD7 in 50% and no expression of CD4. Identical clonal T-cell receptor V gamma-III and V beta gene rearrangments were detected from different areas of hair loss on the right and left thighs. The diagnosis of juvenile patch MF with CD8+ cells was made. The patient was started on antibiotics and ultraviolet B phototherapy.

DISCUSSION

Mycosis fungoides, first described by French dermatologist Jean Louis Alibert in 1806, is the most common of the cutaneous T-cell lymphomas. It is characterized by pleomorphic lesions including patches, plaques, cutaneous tumors, change in pigmentation, or erythroderma rather than with alopecia.[1] Early MF is frequently indistinguishable from eczema or chronic dermatitis, tinea corporis, or even psoriasis and is hypothesized to arise in the setting of persistent antigen stimulation.

Alopecia areata is also a T-cell mediated disorder directed to anagen hair follicles and presenting with non-scarring patchy hair loss that can progress to total alopecia. AA affects both genders and all age groups with 1.7% of the US population estimated to be affected at some time in their lives.[2] About 8% will develop chronic AA.[3] Although the diagnosis is often made clinically, histology shows infiltrates of perifollicular and intrafollicular CD4+ and/or CD8+ T-cells. Recent studies have shown restricted and oligoclonal T-cell repertoires from lesions, suggesting an antigen driven response.[4] A polygenic mode of inheritance with HLA predisposition is thought to underlie AA as in other autoimmune diseases.[5] AA is associated with other autoimmune diseases such as vitiligo, thyroid disease, pernicious anemia, and atopic dermatitis but has not been associated with MF previously.[3]

We have reported two young men who were initially diagnosed with alopecia areata but subsequently developed follicular papules and patches of early MF. Of interest, both had coexisting folliculitis with gram positive cocci and staphylococcus is a putative antigen in MF.[6] Early MF presents with T-cell inflammatory infiltrates in the epidermis (MF), around dermal vessels (MF,Sézary syndrome), or around hair follicles (follicular mucinosis or folliculotropic MF).[7] The degree of lymphocyte atypia and epidermotropism with or without Pautrier's microabscesses (clustering of T lymphocytes around Langerhans' cells) are the criteria required to diagnose early MF.[8] However, cases of folliculotropic MF and syringotropic MF usually lack significant epidermotropism.[9] When mucin is detected and the T-cell infiltrates are not atypical, the terms “follicular mucinosis” or “alopecia mucinosis” are applied and used in literature.

It may be difficult at least initially to distinguish alopecia areata, follicular mucinosis, and follicotropic MF, as shown by these two cases. Whether or not these patients first had AA and then developed MF later or whether this was initially undiagnosed MF is uncertain. We propose considering the existence of a heretofore unrecognized spectrum of benign T-cell proliferation directed to hair follicles (AA) - benign follicular mucinosis - and more definitive malignant cutaneous folliculotropic mycosis fungoides. While immunophenotyping is not helpful, the diagnosis of MF in both patients was supported by the finding of identical T-cell clones from multiple skin sites, as we have previously reported.[10]

Of interest, both MF[11] and AA[12,13] are associated with the same class II DR and DQ human leukocyte antigens (HLA) whose function is to present peptides to CD8 and CD4 T-cells. Although environmental factors and multiple other genes may initiate autoimmune diseases, 50% of the genetic predisposition may be due to the HLA complex genes.[14] HLA antigens may be necessary, although not sufficient, for autoimmunity. HLA- DR3 associations are shared by Grave's disease, Addison's disease, and myasthenia gravis, demonstrating that one HLA molecule can be associated with more than one autoimmune disease.[14,15]

DR5 and its associated DQB1*03 alleles are associated with Alopecia Areata, MF, melanoma, scleroderma, and Hashimoto's thyroiditis.[13]An over-representation of HLA-DRB and DRQ alleles has been reported in patients with AA and MF. HLA-DR5 (DRB1*11) was significantly increased in MF patients (34%) versus controls (11%) for an odds ratio of 3.62.[11]DQB1*03 (301-303) alleles in linkage disequilibrium with DR5 were found in 72% of all CTCL, 67% of MF and 82% of patients with Sézary syndrome versus controls (49%).[11]Recent studies in a Jewish population have also shown DRB1*11 and DQB1*03 to be significantly increased in MF patients.[16] DQB1*03 was significantly increased in familial MF[17] as well as in identical twins, who showed 55% concordancy for alopecia areata.[18] The strongest associations reported for alopecia areata are also HLA alleles DQB1*03 (DQ3) and DRB1*1104 (DR11).[4,12,13,19]Alopecia totalis and alopecia universalis, have been associated with DRB1*04,[20]

DRB1*1104 (DR11),[12, 13] and DQB1*0301 (DQ7).[12, 13, 20,21]

The association of DRB1-1104 and DQB1*03 alleles with MF and AA suggests that these two T-cell mediated immune responses share similar pathogenesis. In summary, patchy hair loss without inflammation (ie AA) may later evolve into folliculocentric or patch stage MF - whether distinct entities or part of a disease spectrum.

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ABBREVIATIONS AND ACRONYMS

Body surface area, BSA

Mycosis Fungoides, MF

Alopecia Areata, AA

Cutaneous T-cell Lymphoma, CTCL

Human leukocyte antigen, HLA

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