Reinstitution of Immune Privilege in Alopecia Areata: Control of Sex Steroid Mediated Inflammation with Norethindrone and Metformin

Colleen Reisz*

Abstract—Alopecia areata (AA) is one of the most common autoimmune diseases, abruptly causing hair loss in men and women. Although AA has been associated with other autoimmune diseases, most individuals are otherwise healthy, and the disease is expressed in one structure, the hair follicle. All aspects of follicle immunobiology are influenced by sex steroids. Below is a case series of women with alopecia areata who regrew their hair by controlling sex steroid directed immunity with a norethindrone containing oral contraceptive, metformin and vitamin D. Limitations: This is a small case series without randomization. Conclusion: Reducing steroidogenesis and aromatase activity with norethindrone containing oral contraceptives and/or metformin led to regrowth of hair in 12 of 14 women with alopecia areata.

Keywords — alopecia areata, aromatase, intracrine, metformin, norethindrone

I. INTRODUCTION

ALOPECIA areata (AA) is an autoimmune disease that targets anagen hair follicles.[1] The disease tends to be abrupt and episodic, peaking between the second and fourth decades of life in both genders. There have been a number of treatments described but none have been found to have consistent or preventive effects. [2]

The role of sex steroids in hair and skin physiology is widely recognized[3][4] Both androgens and estrogens have individual receptors and major differences in tissue distribution.[5] The discovery of the second estrogen receptor, ER-beta, has led to a clearer understanding of specific estrogen action in skin and follicle.[6] ER-beta mediates estrogen action and is found in heavy concentration in the outer root sheath, epithelial matrix and the bulge region of the follicle.[7][8] Aromatase, the rate limiting step in estrogen metabolism, influences communication between androgen and estrogen receptors and is upregulated in inflammation. Upregulation of aromatase leads to androgen depletion and an increase in estrogen metabolites. This distortion in androgen and estrogen ratios leads to depletion of immunomodulatory androgens and an increase in proinflammatory estrogen metabolites. Alopecia areata, characterized by a specific insult to the hair follicle may be provoked by changes in peripheral estrogen metabolism.

In addition to defining the specific location of sex steroid receptors in skin and adnexal structures, there has been research on estrogen effects on macrophage and fibroblast activity.[9] Women undergo cyclic surges of inflammation and hormonal fluctuation which can influence future ovarian cycles, reinforcing and propagating aberrant immune function. In an effort to control and reverse sex steroid influenced immune dysfunction at the hair follicle, 14 females with alopecia areata were given norethindrone or metformin or both and encouraged to take an over the counter vitamin D supplement.

Control of sex steroid production in females is possible with oral contraceptives, metformin and gonadotropin releasing agonists. Metformin, in addition to lowering steroidogenesis, reduces aromatase activity and controls the mechanism involved in maintaining the dormant state of the oocyte pool.[10] Below is a series of female patients who presented to a general dermatology clinic with hair loss. They were not recruited or randomized. After a review of systems that included hormonal status and menstrual cycle history, all were presented with a discussion on what is currently known about inflammation and hormones. They were offered treatments that included one or a combination of birth control pills, metformin and vitamin D.

II. PATIENTS AND METHODS

Fourteen women with AA were evaluated in a general dermatology clinic. Ten of the fourteen patients had recent and abrupt hair loss, presenting for evaluation within one year. Three were seen within one week of noting hair loss. All three evaluated within the first week presented with a single patch on...
the right fronto-parietal scalp and rapidly developed a smaller patch on the ipsilateral vertex. Within four weeks they had developed another patch on the contralateral vertex. Patients were of multiple ethnicities including Caucasian, East Indian, African American, and Asian. This group underwent a hormone directed review of systems that included BMI and menstrual history. Vitamin D levels were drawn in patients who were not on supplements at the time of presentation. The patients were then offered norethindrone containing oral contraceptive pills (1/20 or 1.5/30) or metformin (500-850mg/day) or both, along with vitamin D (1000-2000IU/day). Five patients requested intralosional corticosteroids along with hormonal therapy, and nine patients opted for hormonal treatment only.

III. RESULTS

Response to therapy was seen in 12 of the 14 patients. (Table 1. Age, BMI, duration and Severity of Alopecia Tool (SALT) scores at baseline and follow up) Seven of the 14 had complete regrowth of hair within 12 weeks. Another 4 fully regrew their hair but took at least a year to completely reverse their hair loss. Two continue to have small areas of loss and regrowth in the parietal area on one side of the scalp. One of the 14 patients discontinued treatment due to side effects and converted from a SALT score of 27 to a SALT score of 100 within one week. The older patient with universalis had no response to therapy at a year and has been lost to follow-up.

Several characteristics of regrowth deserve further description. The velocity and density of regrowth were notable, especially in the younger women seen early in the course of disease. The 15 year old with a 10 year history of alopecia totalis had dull, vellus, 2cm long hair in the occiput at baseline. Her initial response to therapy was an immediate change in the occipital scalp, with elongation and sheen. This was the only response for about 16 months, when she started to grow hair on her legs and one axilla. Now, after two years of norethindrone and metformin, she is growing thick and shiny hair on most areas of her scalp except the frontal hairline. The 46 year old presented with withered white and dark hair on the crown but no frontal hair. After several months of metformin only, she regrew her frontal hairline with dense, shiny and pigmented hair. Aromatase distribution varies in the scalp, with prominence in the occiput in both genders and a 6-fold increase in the frontal scalp in women. The regrowth patterns in the 15 and 46 year old suggest that this treatment path initially impacts aromatase. Aromatase expression and tissue promotion may underlie the presentation differences seen in the ophiasis type of alopecia areata.[11]

<table>
<thead>
<tr>
<th>Age/BMI</th>
<th>Fitzpatrick/D-25</th>
<th>SALT score/base line and one year</th>
<th>Duratio of hair loss prior to evaluation</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/25</td>
<td>III</td>
<td>50/0</td>
<td>1 week</td>
<td>M/N/D</td>
</tr>
<tr>
<td>21/20.8</td>
<td>IV/15</td>
<td>10/0</td>
<td>1 week</td>
<td>M/N/D/IL</td>
</tr>
<tr>
<td>14/21.9</td>
<td>I/44</td>
<td>10/0</td>
<td>1 week</td>
<td>N/D/IL</td>
</tr>
<tr>
<td>25/19.1</td>
<td>IV</td>
<td>35/0</td>
<td>4 months</td>
<td>M/N/D/IL</td>
</tr>
<tr>
<td>20/20.4</td>
<td>I</td>
<td>40/10</td>
<td>6 months</td>
<td>M/N/D/IL</td>
</tr>
<tr>
<td>17/21.3</td>
<td>II</td>
<td>6/0</td>
<td>1 year</td>
<td>M/N/D</td>
</tr>
<tr>
<td>19/26.5</td>
<td>I</td>
<td>9/0</td>
<td>4 weeks</td>
<td>M/N/D</td>
</tr>
<tr>
<td>15/23.6</td>
<td>III/34</td>
<td>65/59/43</td>
<td>10 years</td>
<td>M/N/D</td>
</tr>
<tr>
<td>19/22.5</td>
<td>III</td>
<td>27/100/100</td>
<td>3 months</td>
<td>M/N/D/IL</td>
</tr>
<tr>
<td>46/22</td>
<td>II</td>
<td>40/0/0</td>
<td>8 months</td>
<td>M/D</td>
</tr>
<tr>
<td>39/33.3</td>
<td>II</td>
<td>100/100</td>
<td>14 years</td>
<td>M/N</td>
</tr>
<tr>
<td>13/20.7</td>
<td>VI</td>
<td>84/0</td>
<td>2 years</td>
<td>M/D</td>
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<tr>
<td>19/24.8</td>
<td>I/19</td>
<td>25/0</td>
<td>2 months</td>
<td>M/N/D</td>
</tr>
<tr>
<td>63/24.1</td>
<td>II/24</td>
<td>9/0</td>
<td>4 months</td>
<td>M/D/IL</td>
</tr>
</tbody>
</table>

BMI=body mass index, Fitzpatrick phototyping scale I-VI, M=metformin, N=norethindrone containing oral contraceptive, vitamin D-25 ng/ml , IL=intralosional kenalog 5mg/ml at .1ml site, SALT=severity of alopecia tool, D= vitamin D3 supplementation at 100IU/day

IV. DISCUSSION

The science behind sex steroids and immune function is rapidly changing. Recent reviews of sex steroids and immune function yield newer concepts that expand the connections between hormones, inflammation and autoimmunity in both genders.[12] Estrogen is known to favorably impact skin and bone but exhibits proinflammatory effects on the cellular mediators of inflammation, especially fibroblasts and macrophages.
Figure 1a. Alopecia areata: baseline photos in 15 year old with 10 year history

Figure 1b: Alopecia areata: 24 months after norethindrone and metformin

Figure 2: Alopecia areata with full regrowth with metformin 500mg daily for 3 months
Variation in estrogen physiology throughout the body is orchestrated by tissue specific promoters in the human aromatase complex. The fractional conversion of androgens to estrogens is regulated by aromatase that is under local and site specific control. The hair follicle in alopecia areata, being strongly populated by estrogen receptors, may represent a specific alteration in behavior of the aromatase complex.[13]

Women of reproductive age experience variation in endogenous estrogens within and between cycles. The variation in steroidogenesis during the menstrual cycle is accompanied by changes in immune function. Inflammation within one cycle can influence future cycles and propagate aberrancies in immune function.[14][15] The interventions directed towards these women were designed to suppress sex steroid production and lower aromatase behavior.

Clinicians have a number of drugs that affect sex hormone synthesis and immune function in women, including oral contraceptives, gonadotropin releasing agonists and metformin. Oral contraceptives are the mainstay of ovarian suppression. The choice of progestin is important as synthetic progestins vary in their effects on cytokine production.[16] Metformin has widespread effects on steroidogenesis in women with and without polycystic ovary disease.[17] Metformin decreases aromatase activity and influences the mechanisms that control the maturation of oocytes in the ovary. [18][19] Men have less obvious choices for therapy but attention could be directed at aromatase, androgen depletion and inflammation.[20][21][22]

The inclusion of skin color was included as a potential biomarker of vitamin D status, but may also reflect genetic variation in aromatase activity and peripheral estrogen metabolism among the races. [23]

REFERENCES


V. CONCLUSIONS

The hair follicle, richly supplied with estrogen receptors and varying in aromatase expression, may represent a specific target for hormone related inflammatory responses. Targeting peripheral estrogen metabolism may provide treatment options for patients with alopecia areata. Clinicians should include reproductive history and menstrual function in their female patients with autoimmune skin diseases, particularly alopecia areata. The combination of norethindrone and metformin may provide a safe and cost effective approach to hormone related immune dysfunction.

VI. ACKNOWLEDGMENTS

The author thanks Devika Patel, M.D. for assisting with manuscript preparation

Dr. Reisz received her MD degree at the University of Kansas in 1988. She completed her dermatology residency at KU in 1994. Her research interests include alopecia and the effects of polypharmacy in the skin.