Acne Keloidalis Is a Form of Primary Scarring Alopecia

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Objective: To better define the pathogenesis of acne keloidalis (AK).

Design: Prospective, blinded study of histologic material collected from 10 patients with clinically typical AK.

Setting: Outpatient dermatology clinic of a military tertiary care medical center.

Patients: Ten male volunteers 18 years or older with early AK lesions (1- to 4-mm firm papules on the lower occipital/nuchal region).

Data Source: Biopsy specimens from small, early lesions and from clinically uninvolved skin, studied histologically with transverse sectioning.

Intervention: Three separate 4-mm punch biopsy specimens of the scalp (lesional, perilesional, and “normal” scalp) were obtained from each volunteer. The specimens were processed using transverse sectioning.

Main Outcome Measures: The primary variables for data analysis were the presence or absence of the following histologic features: premature loss of the inner root sheath; eccentric placement of shaft, with thinning of the outer root sheath; lamellar fibroplasia surrounding the follicle; loss of sebaceous glands; evidence of follicular destruction or scarring; inflammation; and intrafollicular or perifollicular microorganisms. The number and type of hairs were also recorded.

Results: The most common findings in the 19 histologically abnormal specimens were perifollicular, chronic (lymphocytic and plasmacytic) inflammation, most intense at the level of the isthmus and lower infundibulum; lamellar fibroplasia, most marked at the level of the isthmus; complete disappearance of sebaceous glands, associated with inflamed or destroyed follicles; thinning of the follicular epithelium, most marked at the level of the isthmus; and total epithelial destruction (superficial and deep), with residual “naked” hair fragments. Even some “normal” specimens contained true follicular scars, demonstrating that normal-appearing scalp skin had previously been affected by the disease.

Conclusions: Acne keloidalis is a primary form of scarring alopecia, and many of the histologic findings closely resemble those found in certain other forms of cicatricial alopecia. Extensive subclinical disease may be present in patients with AK and can account for some of the permanent hair loss. Overgrowth of microorganisms does not appear to play an important role in the pathogenesis of the disease. There is no etiologic relationship between AK and pseudofolliculitis barbae. Therapies found to be useful in other forms of inflammatory scarring alopecia are useful in the treatment of early AK.

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SUBJECTS AND METHODS

SUBJECTS

This study was approved by the Clinical Investigation Committee and the Human Use Committee/Institutional Review Board of the Walter Reed Army Medical Center, Washington, DC. All subjects enrolled in the study voluntarily agreed to participate and gave written informed consent.

Ten male volunteers 18 years or older with early AK lesions (1- to 4-mm firm papules on the lower occipital/nuchal region) were recruited from the dermatology clinic of the Walter Reed Army Medical Center. Cases were collected over a 2-year period. Patients who had been treated for AK with oral medications within 6 months or who had large keloidlike nodules or plaques were excluded. If patients had been using topical antibiotics or corticosteroids, there was a 3-week period during which they were off all medications before scalp biopsy specimens were obtained.

METHODS

Three 4-mm punch biopsy specimens of the scalp were obtained from each volunteer. Each biopsy site was anesthetized with 1% lidocaine and 1:100 000 epinephrine. The first biopsy specimen, called lesional, was a discrete papule taken from clinically involved skin on the lower occipital/nuchal region. The second biopsy specimen, called perilesional, was taken from normal-appearing scalp skin, within 1 cm of the lesional specimen. The third biopsy specimen, called normal, was taken from the parietal scalp 4 cm superior to the apex of the left ear. The specimens were placed in 10% formalin and processed using transverse sectioning.16

Multiple levels from each specimen were examined. Specimen labels were coded in a random fashion so that the dermatopathologists were blinded to both the patient and the type of biopsy specimen (lesional, perilesional, or normal skin). Any specimen demonstrating inflammation or scarring was also stained to exclude fungus (periodic acid–Schiff and methenamine silver) and bacteria (Brown and Hoppes, Brown and Brenn). All histologic specimens were reviewed by the same 2 dermatopathologists (L.C.S. and P.S.).

DATA ANALYSIS

The small number of subjects used in this protocol was based on the expectation of a large difference in the histopathologic features of diseased and normal sites and the difficulty in obtaining multiple biopsy specimens from otherwise healthy subjects.

Presentation of data is primarily descriptive, providing results of histopathologic analysis through photomicrographs and a table. The primary variables for data analysis are the presence or absence of the following histologic features: premature loss of the inner root sheath; eccentric placement of shaft, with thinning of the outer root sheath; lamellar fibroplasia surrounding the follicle; loss of sebaceous glands; evidence of follicular destruction or scarring; inflammation (location and type [ie, acute, chronic, or granulomatous]); and intrafollicular or perifollicular organisms (bacteria, fungi, and Demodex). The number and type of hairs found in each specimen were also recorded.

RESULTS

Data on specimens showing abnormal pathologic characteristics are presented in the Table. Nine of 10 specimens from lesional skin, 4 of 10 specimens from perilesional skin, and 6 of 10 specimens from clinically normal skin were histologically abnormal. The most consistent findings among these 19 histologically abnormal specimens were as follows: perifollicular chronic (lymphocytic and plasmacytic) inflammation, most intense at the level of the isthmus and lower infundibulum (n = 18; Figure 1); complete disappearance of sebaceous glands associated with inflamed or destroyed follicles (n = 16); thinning of the follicular epithelium, most marked at the level of the isthmus (n = 15; Figure 2); lamellar fibroplasia, most marked at the level of the isthmus (n = 14; focal or total epithelial destruction (superficial and deep), with residual “naked” hair fragments (n = 11; Figure 3); dilatation of the follicular canal extending down to or below the isthmus (n = 4; Figure 4); premature desquamation of the inner root sheath affecting at least 1 follicle (n = 3; Figure 4); and acute (neutrophilic) inflammation surrounding degenerating follicular components (n = 2).

One lesional specimen was histologically normal, except for the presence of mild perifollicular epidermal spongiosis and chronic superficial perivascular inflammation. This could account for the palpability...
of the lesion that was selected for biopsy. This lesion was felt to be unrelated to the patient’s AK and highlights one of the pitfalls of selecting very early lesions for examination.

Those few follicles that demonstrated premature desquamation of the inner root sheath all showed marked degenerative changes. Therefore, this inner root sheath change was not an early finding. Acute inflammation, when present, was found only at the level of the infundibulum and was always associated with total destruction of the epithelium at that level. Small numbers of Demodex organisms were found in 5 of the 30 specimens studied (normal, n = 1; perilesional, n = 2; and lesional, n = 2). All the organisms were found within sebaceous ducts, and only one of the affected follicles showed any degree of inflammation. Only rare spores (presumably Pityrosporum) were identified in specimens showing inflammation or scarring. A few colonies of gram-positive cocci were present in the scale/crust on the epidermal surface of the acutely inflamed follicles. However, bacteria were rare in the follicular canals and absent in the perifollicular region of all specimens.

Despite the fact that the selected biopsy sites appeared to be clinically normal, 4 of 10 perilesional and 6 of 10 normal specimens showed at least one follicle with marked abnormalities. The changes were similar to those found in the lesional specimens, but, in general, the findings were less dramatic. However, even the normal specimens contained true follicular scars (Figure 5), demonstrating that normal-appearing scalp skin had previously been affected by the disease.

PATHOGENIC ABNORMALITIES IN 10 PATIENTS WITH ACNE KELOIDALIS

<table>
<thead>
<tr>
<th>Lesion No. (Patient No.)</th>
<th>Chronic Perifollicular Inflammation</th>
<th>Complete Disappearance of Sebaceous Glands</th>
<th>Thinning of the Follicular Epithelium</th>
<th>Lamellar Fibroplasia</th>
<th>Focal or Epithelial Destruction</th>
<th>Dilatation of the Follicular Canal</th>
<th>Premature Desquamation of the Inner Root Sheath</th>
<th>Acute Inflammation</th>
<th>No. of Follicles</th>
<th>No. of Inflamed Follicles</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 (2)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>L3 (5)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>L4 (1)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>L5 (6)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>L6 (8)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>L7 (10)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>L8 (9)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>L9 (4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>L10 (5)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td><strong>Perilesional Scalp Biopsy Specimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 (6)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>P2 (9)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>P3 (5)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>P4 (2)</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>“Normal” Scalp Biopsy Specimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 (10)</td>
<td>+ (Mild)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>N2 (5)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>N3 (6)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>N4 (8)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>N5 (1)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>N6 (4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Total No. Positive (n = 19)</td>
<td>18/19</td>
<td>16/19</td>
<td>15/19</td>
<td>14/19</td>
<td>11/19</td>
<td>4/19</td>
<td>3/19</td>
<td>2/19</td>
<td>Mean, 14</td>
<td>Mean, 3</td>
</tr>
<tr>
<td>Normal specimens, pooled data (n = 11)</td>
<td>0/11</td>
<td>0/11</td>
<td>0/11</td>
<td>0/11</td>
<td>0/11</td>
<td>0/11</td>
<td>0/11</td>
<td>0/11</td>
<td>Mean, 16</td>
<td>0/11</td>
</tr>
</tbody>
</table>

* Plus sign indicates present; minus sign, absent.

COMMENT

Well-established lesions of AK that are examined in standard vertical sections reveal dense dermal fibrosis without evidence of keloid formation, as well as chronic inflammation and the presence of many plasma cells. Hair follicles are disrupted, and microabscesses and/or foreign-body reactions surround hair shafts. There is a conspicuous absence of sebaceous glands in well-developed lesions.3,5

Herzberg and colleagues15 described papular lesions of AK using transverse sections in an attempt to characterize the evolution of the disease. They evaluated 7 discrete papules from the occipital scalp of 4 patients and found that inflammation was most marked at the level of the lower infundibulum and isthmus of the follicle. The character of this inflammation changed from being more acute at the upper levels of the infundibulum to chronic and granulomatous at a deeper level (isthmus). Overall, there was a paucity of sebaceous glands.
at any stage of the inflammation. Based on their findings, the authors propose the following sequence of inflammatory events: Acute inflammation begins in the deep infundibulum or isthmus or perhaps in the sebaceous gland. This weakens the follicular wall; subsequently, hairs are released into the dermis. The naked hairs stimulate a foreign-body reaction with acute and chronic granulomatous inflammation. Subsequent fibrosis occurs within the dermis, which then might distort and occlude the follicular lumen and consequently lead to hair retention within the deeper follicle. This then leads to further inflammation and scarring. The role of Demodex was considered but not substantiated.

We have been able to confirm and expand the findings of Herzberg and colleagues. Furthermore, we can establish AK as a form of primary inflammatory scarring alopecia. The earliest changes seen, found in visible lesions as well as nonlesional scalp skin, affect isolated follicles or a single follicular unit. Affected follicles either are destroyed or undergo repair as inflammation subsides. The small papular lesions of AK represent follicles affected by marked inflammation and edema. However, a spectrum of subclinical disease exists in which many follicles can be affected by relatively mild inflammation.

We propose the following pathogenesis, based on our findings in both clinical and subclinical disease. Antigens of the follicular epithelium or within the follicular canal attract perifollicular inflammatory cells at the level of the isthmus. Potential intrafollicular antigens include Demodex, normal skin flora (fungal spores and bacteria) and their metabolic by-products, cosmetics, sebum, and desquamated keratinocytes. Acne keloidalis is a disease of adulthood, suggesting that candidate antigens are those that are more prominent after puberty. The sebaceous gland is either an early target of inflammation or an “innocent bystander” that is destroyed early in the inflammatory process. Perifollicular inflammation alters or weakens the follicular wall and is manifested first by spongiosis and mild lymphocytic exocytosis.
tosis. This weakened epithelial wall may then become increasingly “leaky” to intrafollicular antigens, amplifying the inflammatory reaction. A reparative attempt ensues, in the form of concentric lamellar fibroplasia. The hair shaft eventually migrates through the weakened follicular wall and enters the dermis, inciting intense inflammation and epithelial destruction. A follicular scar is the result. Hair shaft fragments and degenerating epithelial components incite hypertrophic scarring in some individuals, resulting in a keloidal tissue reaction. This chain of events can be broken at any point (spontaneously or with treatment), allowing for at least partial follicular healing. This accounts for viable follicles surrounded by lamellar fibroplasia with loss of sebaceous glands.

The suggestion made by Herzberg et al\textsuperscript{15} that the presence of \textit{Demodex} might be related to the pathogenesis of the disease was not supported but certainly not entirely disproved by our findings. Similarly, we found little evidence to support the role of pathogenic bacteria in the pathogenesis of AK, although histopathologic analysis is a poor tool for studying small numbers of bacteria and their sometimes potent antigens. However, we have clearly established that ingrown hairs, as found in pseudofolliculitis barbae, play no role in the cause of this condition. The histologic features of pseudofolliculitis barbae have been well described.\textsuperscript{14} A short distance from the follicular apparatus or within the upper portion of the infundibulum, there is external penetration of the curved hair shaft into the skin. The process is simply that of a foreign-body reaction, with the tip of the hair shaft acting as the foreign body. This is totally unlike the situation with AK, and the notion that AK and pseudofolliculitis barbae share a common pathogenesis is erroneous and should be abandoned.

Acne keloidalis can be considered to be a bona fide member of the scarring alopecia family of disorders. Most of the histologic findings seen in early AK are virtually identical to those found in another form of primary scarring alopecia, namely central centrifugal scarring alopecia (CCSA), also known as the follicular degeneration syndrome,\textsuperscript{17,18} hot-comb alopecia,\textsuperscript{17,19} and pseudopelade of the vertex/crown.\textsuperscript{20,21} This does not imply that AK is the same disease as CCSA since different diseases commonly result in similar histopathologic changes. A relationship between the 2 conditions may exist, however, because both tend to predominate in the African American population, and they commonly coexist in the same patient (\textbf{Figure 6} and \textbf{Figure 7}).

The histologic similarities between AK and CCSA also suggest a similar approach to therapy. In our experience, the combination of potent topical cortico-
roids, such as fluocinonide, along with prolonged use of an oral antibiotic, such as tetracycline, is of considerable benefit in the treatment of both CCSA and AK. Both conditions are characterized by rather extensive subclinical disease and are chronic and progressive, requiring long-term prophylactic treatment.

The keloidal masses seen in some patients with AK represent a peculiar host response to degenerating follicular components and the resultant inflammation. Once the integrity of the follicular epithelium is violated, a nidus for superinfection is created. Bacterial overgrowth incites further tissue inflammation and damage, and the resulting tissue swelling and fibrosis trap both viable and disintegrated follicles in a hypertrophic scar. Trapped hair shafts and epithelium elicit a foreign-body granulomatous reaction and provide a site for ongoing infection. These changes, although they represent a dramatic manifestation of the disease, are secondary events and unrelated to the events that initiate the disease. In many patients, the disease behaves like other forms of scarring alopecia, with patches of hair loss separate from any papulonodular lesions (Figure 8). In theory, if early disease could be prevented or effectively treated, the chronic keloidal component of AK would not occur.

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