Actinic Granuloma is a Unique and Distinct Entity: A Comparative Study With Granuloma Annulare

[Original Articles]

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Abstract

Since the initial description of actinic granuloma (AG), debate has continued over whether it should be considered a specific condition or simply granuloma annulare (GA) located in sun-exposed areas of skin. We conducted a case-control study to clarify this issue. Twenty cases given the diagnosis of AG between 1991 and 2001 were retrieved from our archives. We applied the following inclusion criteria: extensive loss of elastic tissue in or at the side of the granuloma, and elastophagocytosis. Sixteen cases of GA that involved sun-exposed and non-sun-exposed sites, 8 cases from each group, were randomly selected as controls. Histologic parameters were quantitated on hematoxylin-eosin, Verhoeff van Gieson, and Alcian blue stains for each case. Results were statistically analyzed by SPSS program version 9. Fourteen cases of AG met our inclusion criteria. Presence of mucin, occurrence of multinucleated giant cells, and the type of granulomata were of high statistical significance ($p < 0.01$) in distinguishing the two entities. We also found that the location of the granulomata in these conditions is different and of statistical significance ($p < 0.05$). Based on histomorphology, we believe that AG should be considered a separate, independent condition and should be distinguished from GA even in sun-exposed areas of skin.

Although reports of granuloma annulare (GA) in sun-exposed areas of the skin have appeared since 1961 (1), actinic granuloma (AG) was first named as a distinct entity in 1975 (2). A consensus has not been reached on the exact nosology of AG. Most investigators believe it to be a unique and distinct entity (3–6); some consider it simply to be GA in sun-exposed skin (7). However, there have been no controlled studies to examine histologic similarities and differences between both conditions in sun-exposed and non-sun-exposed locations.

We attempt to evaluate the histologic features of AG and compare them with GA in both types of sites.
MATERIALS AND METHODS

As clinical features of AG are often indistinguishable from those of classic GA, we used only histologic definitions for the diagnosis of AG and GA. Twenty cases of AG were retrieved from the archives of the Department of Pathology at the University of British Columbia from 1991–2001. Fourteen cases met our inclusion criteria: sufficient tissue for elastic and mucin stains, a zone of granulomatous inflammation with loss of elastic tissue in or at the side of the granuloma, and elastophagocytosis. As controls, we randomly selected sixteen cases of GA, 8 involving sun-exposed and 8 involving non-sun-exposed sites of the body. We developed a series of histomorphologic features to be examined in all cases by hematoxylin-eosin, Verhoeff van Gieson, and Alcian blue (pH 2.5) stains. The features included depth (superficial, deep, or both), and type (palisading, interstitial, or sarcoidal), of the granuloma. Presence and absence of multinucleated giant cells and scars were assessed. The inflammatory cell population (eosinophils, mast cells, plasma cells, and neutrophils) was examined. Quantitative assessment of mucin was performed within the zone of granulomatous inflammation. To ensure that the 8 control cases of GA on sun-exposed skin originated from sites with chronic actinic damage, the degree of solar elastosis in a noninflamed portion of each biopsy was assessed semiquantitatively as: absent, mild (smudging of elastic fiber outlines in the superficial dermis, with increased affinity for hematoxylin and decreased affinity for Verhoeff stains), moderate (confluence of abnormal elastic fibers with reduction in intervening collagen), or marked (complete replacement of superficial dermal collagen by a band of abnormal elastic tissue). Clinical features were not reviewed. Results were analyzed statistically by SPSS program version 9.

RESULTS

The uniform presence of multinucleated giant cells in AG and their reduced frequency in GA was found to be a distinguishing feature of very high statistical significance ($p < 0.01$). While mucin deposition is typically present in GA, dermal mucin is not noticeably increased within zones of granulomatous inflammation in the majority of cases of AG; this discriminating feature also has very high statistical significance ($p < 0.01$). The type of granuloma also differs in these two conditions. In AG, the granulomata are sarcoidal and interstitial, but the palisading granulomata typical of GA are not seen ($p < 0.01$). In contrast, the GA granulomata are usually palisading or interstitial. Thus the identification of a palisading or sarcoidal pattern of granulomatous inflammation may be helpful in distinguishing these two entities; however, if the granulomatous inflammation has an entirely interstitial pattern, other histologic features must be used to assist in the distinction. While granulomata typically involve both the superficial and deep dermis in GA, they are confined to the superficial dermis in AG ($p < 0.05$). We could not discern a definite scar on a histologic basis in most cases of AG. There was a trend toward a greater number of eosinophils in AG than GA, which did not reach statistical significance. We could not appreciate loss of elastic fibers or elastophagocytosis in any cases of GA, even those on sun-exposed skin with solar elastosis. All 8 cases of GA on sun-exposed skin demonstrated solar elastosis; this was quantitated as mild in 3 and moderate in 5.

DISCUSSION

Since its initial description (2), AG has been documented in several case reports and small case series (3–6). While most of these descriptions intended to demonstrate it as a distinct entity unrelated to GA, Ackerman maintains the
opinion that it should be considered simply as GA in sun-exposed areas of skin (8), arguing the nonspecificity of the O'Brien criteria for AG (7). In spite of conflicting views, no controlled studies have compared the histologic features of AG and GA in both sun-exposed and non-sun-exposed areas. In the current study, we attempt to clarify this dilemma.

Unfortunately, there are no clinical features reliable enough in discriminating these two conditions from one another to act as a gold standard in corroborating histologic observations. The demographics of reported patients initially suggested fair skin, freckling, advanced age, and, of course, chronic actinic damage as codependent predisposing factors (2,3,9). When multiple lesions are present, they usually have been confined to sites of chronic actinic damage (2,9). However, lesions clinically and histologically indistinguishable from AG and distinct from GA subsequently have been described confined to sun-protected skin in some patients (10,11). The morphology of an individual lesion of AG has been characterized as a smooth elevated faintly erythematous papule which gradually expands to form an asymptomatic annular plaque up to several centimeters in diameter with occasional slight central atrophy or hypopigmentation (2,3). This morphology does not allow distinction from papular and annular forms of GA. Thus, if AG and GA are distinct from one another, this distinction will depend upon the identification of histologic differences rather than resting on the clinical setting.

We have observed a number of histologic features (Table 1) that are of significance in discriminating the two processes and also suggest that pathogenetic events are distinct rather than overlapping. Multinucleated giant cells were found in large numbers in our cases of AG (Fig. 1) in concordance with previous descriptions (3,4). However, there were no asteroid bodies as demonstrated in O'Brien's first report (2). Absence of mucin in AG as compared with GA was a striking difference in most cases and would be a useful criterion for differentiation. This finding has not been described clearly in previous reports. One of our three AG cases with moderate mucin was found adjacent to a basal cell carcinoma, which may have contributed to this degree of mucin. None of the AG cases showed a prominent degree of mucin deposition. In addition, the predominant type of granuloma was found to be different in AG compared to GA. Sarcoidal granulomata were observed in the majority of cases of AG (Fig. 2), while no cases of AG showed palisading granulomata; this pattern of granulomatous inflammation in AG is as previously described (5). However, an interstitial pattern of granulomatous inflammation was seen in both AG and GA, and was not found to be a helpful feature in the differential diagnosis. Moreover, we demonstrated that in most cases of AG the granuloma is confined to the superficial dermis at the level of the solar elastosis, in contrast to GA in which the granulomata are found in both the superficial and the deep dermis. We did not find the presence of a scar to be a helpful feature in diagnosing AG, in contrast to a previous report (4). Of interest, we noted neither elastophagocytosis nor loss of elastic fibers in any of the cases of GA, regardless of location on sun-exposed or sun-protected skin, unlike AG (Figs. 3, 4).
TABLE 1. A comparison of histologic features of actinic granuloma and granuloma annulare
AG, actinic granuloma; GA-s, granuloma annulare in sun-exposed sites; GA-ns, granuloma annulare in non-sun-exposed sites; MNGCs, multinucleated giant cells.

<table>
<thead>
<tr>
<th>Histologic features</th>
<th>AG (n = 14)</th>
<th>GA-s (n = 8)</th>
<th>GA-ns (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) MNGCs</td>
<td>14 (100%)</td>
<td>5 (62%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>2) Mucin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>9 (65%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>2 (14%)</td>
<td>0</td>
<td>1 (12%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (21%)</td>
<td>4 (50%)</td>
<td>5 (62%)</td>
</tr>
<tr>
<td>Marked</td>
<td>0</td>
<td>4 (50%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>3) Granuloma type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoidal</td>
<td>8 (57%)</td>
<td>2 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial</td>
<td>6 (43%)</td>
<td>0</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Palisading</td>
<td>0</td>
<td>6 (75%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>4) Granuloma location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial only</td>
<td>11 (79%)</td>
<td>2 (25%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Superficial and deep</td>
<td>3 (21%)</td>
<td>6 (75%)</td>
<td>5 (62%)</td>
</tr>
<tr>
<td>Deep only</td>
<td>0</td>
<td>0</td>
<td>1 (12%)</td>
</tr>
</tbody>
</table>

AG, actinic granuloma; GA-s, granuloma annulare in sun-exposed sites; GA-ns, granuloma annulare in non-sun-exposed sites; MNGCs, multinucleated giant cells.

FIG. 1. Multinucleated giant cells of Langhans and foreign-body types in actinic granuloma (hematoxylin and eosin).

FIG. 2. Sarcoidal granulomata in actinic granuloma (hematoxylin and eosin).
There have been reports demonstrating lesions identical to AG on non-sun-exposed areas, with the term “annular elastolytic giant cell granuloma,” which some believe is a “more appropriate, easily understandable and descriptive term,” designated for such occurrences (10,11). However, O’Brien refuted this term “for the main reason that it conceals the intrinsic and true nature of the lesion, that is, it represents an inflammatory reaction in response to actinically degenerate elastic tissue” (12).

It is noteworthy that few attempts have been directed toward understanding the pathogenesis of AG. In his immunocytochemical studies, McGrae (3) suggests a cell-mediated immune response to elastotic tissue as a possible disease mechanism in AG. In addition, he noted enzymatic differences between histiocytes of AG and GA, supporting the authenticity of AG as an entity distinct from GA. He postulated that some of the cases reported as GA that occurred exclusively in sun-exposed areas of the skin may have actually represented AG. The theory that elastic tissue alteration plays an essential role in the pathogenesis of AG has also been supported by reports of AG associated with relapsing polychondritis (13) and perforating pseudoaxanthoma elasticum (14).

Detailed histologic examination of our 14 cases of AG demonstrates features that permit discrimination from GA, and also provides insight into pathogenetic mechanisms that are distinct from those of GA. In GA, the occurrence of palisading granulomata suggests an inflammatory response to persistent and relatively large aggregates of material, as in the histologically similar settings of ruptured epidermoid cyst, gout and rheumatoid nodule. This would be expected in GA as a reaction to nodules of altered collagen. The reaction is expected to occur throughout the superficial and deep dermis without regard for location of the collagen. In contrast, the sarcoidal granulomata and multinucleated giant cells of
AG suggest an inflammatory response directed toward smaller materials, such as individual altered elastic fibers, that are more readily destroyed to the point where they are no longer visible by light microscopy. The confinement of the inflammatory reaction to the superficial dermis, corresponding to the zone of solar elastosis, supports the original hypothesis that elastotic material altered by chronic sun exposure is the specific target in this disorder (2,5,12).

In summary, we have demonstrated that AG can be identified based on histologic features that are different from those seen in GA, and believe that those who diagnose and treat diseases of the skin should consider AG and GA distinct entities.

REFERENCES


Key Words: Actinic granuloma; Granuloma annulare; Elastophagocytosis