Report

Frontal fibrosing alopecia versus lichen planopilaris: a clinicopathological study

Enrique Poblet, MD, Francisco Jiménez, MD, Alejandro Pascual, MD, and Enric Piqué, MD

Abstract

Background Frontal fibrosing alopecia (FFA) is an acquired scarring alopecia currently considered a clinical variant of lichen planopilaris (LPP). Our purpose was to examine the clinicopathological features of FFA. In addition, we investigated the similarities and differences between FFA and LPP.

Methods Biopsies from the scalp lesions of eight patients with FFA and eight patients with LPP were microscopically analyzed. Two cases of FFA and four cases of LPP were studied using direct immunofluorescence.

Results In spite of the completely different clinical characteristics of FFA and LPP patients, the histopathological findings for the two entities were similar. Common microscopic findings for both FFA and LPP included an inflammatory lymphocytic infiltrate involving the isthmus and infundibulum of the hair follicles, the presence of apoptotic cells in the external root sheath, and a concentric fibrosis surrounding the hair follicles that resulted in their destruction with subsequent scarring alopecia. Biopsies taken from FFA patients showed less follicular inflammation and more apoptotic cells than those from LPP patients. In some cases of LPP, the inflammatory infiltrate involved the interfollicular epidermis, a finding never present in our FFA cases. Direct immunofluorescence was negative in the two cases of FFA studied and showed deposits of immunoglobulins and/or complement in two of the four LPP cases examined.

Conclusions The characteristic findings for FFA were more prominent apoptosis and less inflammation than found in LPP, along with spared interfollicular epidermis. FFA cases showed a rather characteristic histopathological pattern, although we could not find any clear-cut histological differences between FFA and LPP.

Introduction

Frontal fibrosing alopecia (FFA) is a progressive scarring alopecia first described by Kossard in 1994. Patients are usually elderly postmenopausal women who present a symmetric recession of the frontal and temporal hairlines. The affected skin appears pale and atrophic, lacking follicular orifices. A common associated finding is a bilateral loss of the hair of the eyebrows. The course of this disease is slowly progressive, and medical therapies have not been efficacious in the majority of patients. Since its original description, numerous reports have appeared in the literature, suggesting that FFA is more prevalent than originally thought.

Most authors consider FFA as a clinically distinct variant of lichen planopilaris (LPP), based on the fact that their histological findings appear to be indistinguishable. Both entities show a lichenoid lymphocytic inflammatory infiltrate, perifollicular fibrosis, and hair follicle destruction. It is thought that the destruction of the external root sheath at the level of the isthmus (where the stem cells are supposed to reside) is responsible for the nonreversible scarring type of alopecia.

This comparative study of FFA and LPP was undertaken with the goal of determining whether there are histopathological differences between the two conditions that could allow a diagnosis to be made solely on the histological picture.

Materials and Methods

The case records of seven women with FFA diagnosed in the Canary Islands and one woman with FFA diagnosed at the Hospital General Universitario de Albacete between 1998 and 2002 were reviewed. The clinical diagnosis was confirmed in all patients with scalp biopsies obtained from the affected areas. The biopsies were analyzed in vertical and horizontal sections, stained with hematoxylin-eosin, periodic acid Schiff (PAS) stain, and Masson's trichrome stain. Two cases were analyzed with direct immunofluorescence for immunoglobulin A (IgA), IgG, IgM, C3 complement, and fibrinogen.
In addition, eight scalp biopsies of lichen planopilaris were retrieved from the archives of the Pathology Department of the Hospital General Universitario de Albacete, in order to compare their histopathological findings with those of FFA. These cases were also stained with hematoxylin-eosin, PAS stain, and Masson’s trichrome stain. Direct immunofluorescence was performed in four out of eight cases.

For evaluation of the histopathological signs, a semiquantitative analysis was used, with grading from negative (−), through mild (+) and moderate (++), to severe (+++).

**Results**

**Clinical findings for eight patients with FFA**

The clinical data for the eight patients with FFA are summarized in Table 1. The age of onset of the alopecia ranged from 55 to 84 years (mean age 68 years). Four patients (50%) came to our dermatology clinic requesting a consultation for a different pathology, not related to their hair loss problem. On physical examination, all patients showed the typical recession of the frontal and temporal hairlines, bilaterally and symmetrically (Fig. 1). At the hairline, some follicular orifices of the existing hairs showed signs of follicular hyperkeratosis. This early sign could be better seen with loupe magnification. The hair shafts of these affected hyperkeratotic follicles could be easily pulled out with forceps. A very typical diagnostic sign in all our patients was the contrast in the skin pigmentation between the areas of alopecia, uniformly pale and devoid of follicular orifices, and the hyperpigmentation of the sun-damaged forehead skin (Fig. 2).

In one patient, the areas of fibrosing alopecia also involved the occipital posterior hairline (Fig. 3). Six of the eight patients presented a bilateral loss of the eyebrows to some degree. No mucocutaneous lesions of lichen planus were found at other sites.

Laboratory work-up was unremarkable in all patients. Medical therapies including topical corticosteroids, intra-

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age at diagnosis (years)</th>
<th>Age of onset (years)</th>
<th>Eyebrow alopecia</th>
<th>Axillary alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>64</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>54</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>55</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>53</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>79</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>65</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>73</td>
<td>60</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>55</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*All patients were female.*
lesional triamcinolone, and topical 5% minoxidil were tried, but no clear response was obtained in any of the patients.

The severity and course of the alopecia were more progressive in some patients than in others. Most patients covered their fronto-temporal recession by hair styling. However, one patient required a wig.

**Histopathological findings for FFA and LPP (Table 2)**

**Lichenoid/interface lymphocytic inflammatory infiltrate**

A lymphohistiocytic inflammatory infiltrate, mainly localized at the isthmus and infundibulum area of the hair follicles, was a common finding of LPP and FFA (Fig. 4). The inflammatory infiltrate had lichenoid characteristics, although the severity of the infiltrate was variable. In general, the lichenoid tissue reaction was milder in FFA than in LPP. Cases of LPP with severe inflammation completely obscured the basal layer of follicular keratinocytes. In all cases of FFA examined, the damage to the basal cell layer was subtler, and the inflammatory infiltrate tended to permeate the outer root sheath without marked damage to the basal cells (Fig. 5). This finding could be better seen in horizontally oriented tissue sections.

In addition to the follicular inflammation, a superficial perivascular lymphohistiocytic inflammatory infiltrate could be seen...
in the cases of LPP. In the FFA cases, this infiltrate was not seen, or consisted only of a few lymphocytes or melanophages.

**Apoptosis**
A very prominent and characteristic finding in FFA was the eosinophilic necrosis of cells of the external root sheath (apoptotic cells). Apoptosis in FFA is prominent at the isthmus and can even appear at the infundibulum (Fig. 6). In LPP, the presence of apoptotic cells was usually not as prominent as in FFA and, when present, apoptotic cells were located primarily at the lower part of the hair follicle.

**Lamellar or perifollicular fibrosis**
Lamellar or perifollicular fibrosis could be found in both LPP and FFA, involving the same part of the follicles as the inflammatory infiltrate (Fig. 7).

**Infundibular dilatation and infundibular hypergranulosis**
Infundibular dilatation and infundibular hypergranulosis were found in both diseases, to similar degrees.
Direct immunofluorescence
The two cases of FFA tested were negative for immunoglobulins, complement and fibrinogen. Two cases of LPP showed granular IgG deposits along the epidermal and follicular basal membrane zone. In addition, one of these cases showed staining of colloid bodies with IgA and IgM.

Discussion
Although FFA was first described just a decade ago, the increasing number of cases reported lately in the literature seems to indicate that this disease is underrecognized. One reason for this is that the disease mainly affects women over 60, who consider this type of hair loss a consequence of the normal process of aging. As a result, a significant portion of patients do not bother requesting a consultation for this problem, especially in the early stages of the disease. As a matter of fact, 50% of our FFA patients came to our clinic for another skin problem not related to their hair loss.

The etiology of FFA remains a mystery. Although the disease has been termed 'postmenopausal frontal fibrosing alopecia', it has also occasionally been reported in premenopausal women. FFA fails to respond to hormone replacement therapy, and there is no evidence to implicate a hormonal basis as its cause. Although anecdotal associations of FFA with other entities such as lateral oophorectomy have been reported, no consistent associations have been demonstrated.

Our FFA patients presented the four typical clinical signs previously reported in the literature: (1) a symmetric and progressive recession of the frontal and temporal hairlines, described as a band-like pattern of alopecia; (2) follicular hyperkeratosis of the existing hairs; (3) pale and atrophic skin devoid of follicular orifices in the zone of alopecia, contrasting with the hyperpigmented sun-damaged skin of the forehead; and (4) marked decrease or complete loss of the eyebrows. In one of our patients, the zone of alopecia also affected the occipital hairline, an observation not reported in the literature. In contrast, the clinical picture of LPP usually consists of multifocal areas of scarring alopecia with perifollicular erythema that appear throughout the scalp, most commonly in the vertex and parietal areas. LPP may be associated with lichen planus at other sites in up to 50% of patients. In contrast, as far as we know, only two cases out of the nearly 40 cases of FFA reported in the literature have been associated with lesions of oral or cutaneous lichen planus.

In spite of their completely different clinical pictures, based on histopathological findings, FFA is currently considered a clinical variant of LPP. Both entities show a lymphocytic infiltrate obscuring the interface between the follicular epithelium and dermis and involving the upper mid portion of the follicle (infundibulum and isthmus), infundibular dilatation, perifollicular fibrosis, apoptotic cells in the external root sheath, and hair follicle destruction.

Based on our observations, if we had to indicate histological differences between FFA and LPP, we would state that, in general, FFA tends to show much more apoptosis and less inflammatory infiltrate than LPP. These differences, however, may vary according to the stage of the disease, as well as the type of lesion biopsied. Some cases of LPP showed intense damage of the basal cell layer, a feature not observed in our FFA cases. In addition, in FFA we could not find significant superficial perivascular lymphohistiocytic infiltrate. However, this infiltrate was present in all cases of LPP. In our study, 50% of the LPP cases showed interfollicular lichenoid changes. This sign, as well as the presence of direct immunofluorescence deposits, supports the diagnosis of LPP. However, due to the small sample size of our immunofluorescence study, further studies will be needed to draw definite conclusions.

In summary, although the histological pattern of FFA is suggestive of the diagnosis, we have not found enough histological differences to enable FFA and LPP to be differentiated based solely on the histopathological picture. However, in our opinion, whether FFA can be considered a variant of LPP just because they share a common inflammatory reaction pattern is still questionable. We have to bear in mind that the histo-
logical changes of LPP cannot be considered diagnostic. For example, the scarring alopecia of LPP and lupus erythematosus may resemble each other histologically, and some cases of androgenic alopecia may also exhibit a lichenoid reaction pattern. Moreover, a lichenoid epidermal reaction can be found not only in lichen planus but also in nosologically unrelated dermatoses, such as certain types of drug reactions, or graft versus host disease. Thus, we prefer to consider FFA as one of the causes that may produce the histological pattern that has been called lymphocyte-associated primary scarring alopecia or a specific type of lymphocytic cicatricial alopecia.

References