Lichen Planopilaris-histologic Criteria & Clues in Vertical Sections

Michael Wilk*, Bettina G. Zelger and Bernhard Zelger

1 Dermatohistological Laboratory and Private Practice, Nuernberg, Germany
2 Institute of Pathology, Medical University Innsbruck, Austria
3 Clinical Department of Dermatology & Venerology, Medical University Innsbruck, Austria

Abstract

We report on our histological experience in 47 patients with lichen planopilaris/frontal fibrosing alopecia. Besides presenting the spectrum of clinical appearance of the disease we emphasize the importance of vertical histologic sections of biopsies in the clinicopathological work-up of these patients and give precise histologic criteria and clues in different stages of the disease. Immunohistologically, we found a marked reduction of epithelial Ki-67 expression next to the inflammatory process especially evident in advanced stages of disease.

Keywords: Lichen planopilaris; Frontal fibrosing alopecia; Dermatopathology

To the Editor

Lichen planopilaris (LPP) is considered to represent a variant of lichen planus which predominantly affects the scalp. In LPP cutaneous lesions elsewhere on the body except the scalp have been reported in up to 50% of cases [1-4], before, concurrent as well as after the onset of LPP [1]. Mucous membranes, nails as well as hair-bearing and non-hair-bearing areas of the body have been reported to be involved, and this may sometimes be helpful when the diagnosis of LPP is in doubt or difficult from a clinical and/or dermatohistopathological point of view. Clinically, LPP presents as a multifocal, reticulated area of hair loss with perifollicular erythema sometimes accompanied by scales. Individual hairs may be preserved. In the time the disease leads to follicular hyperkeratosis, follicular fusion, whitish scarring with loss of follicular orifices and mottled hyperpigmentation. The disease may also present as frontal fibrosing alopecia (FFA) [5-10] and Graham-Little-syndrome when eyebrows, axillae and/or pubic hair are involved as well combined with widespread keratotic papules on the trunk and extremities (Figure 1). While the simultaneous occurrence of LPP and FFA has been reported in up to 14% of patients [6], scalp involvement in the latter tends to be localized and not multifocal, occurs mostly in postmenopausal women and is only rarely associated with lesions of lichen planus [5-10]. However, eyebrow and especially upper limb alopecia with scarring appear to be more common in FFA than previously reported [10]. Thus, lichen planus, LPP and FFA appear to represent a spectrum of disease with clinical overlap and similar histological features. Both, LPP and FFA tend to scarring alopecia which makes the accurate diagnosis an urgent and important matter.

In contrast to lichen planus, LPP and FFA are much more commonly reported in women [1-4,8,11,12]. This is similar to lupus erythematosus and other autoimmune disorders which are more commonly seen in (young) women. Alternatively or complementary to the above, this may be an underestimate of the true prevalence in men due to the fact that women to some degree more frequently seek medical advice because of hair loss and the simultaneous occurrence of common baldness in men, possibly in part patients with fibrosing alopecia in male pattern distribution. The difference in gender is also reflected by our study of 39 women and 8 men diagnosed to suffer from LPP/FFA at the outpatient clinic/histological laboratory of the Department of Dermatology University of Innsbruck (n=37) or sent as histologic consultation cases (n=10) between 2006 and 2013. The average age of men and women at presentation was also different with 55 (range 27-78) and 42 (range 23-67) years, respectively.

Despite advances in diagnostic procedures using microarray analysis and new insights into possible pathogenetic factors in primary cicatricial alopecia (such as loss of immune protection of stem cells, lipid metabolism dysregulation, impaired self-maintenance of hair...
follicle stem cells, increased apoptosis, enhanced autoimmunity by pro-inflammatory cytokines and environmental/genetic predisposition, neurogenic skin inflammation) the precise mechanisms that provoke the destructive reaction to the hair follicle, including LPP and FFA, remain to be elucidated [13,14]. Thus, at present primary cicatricial alopecias are best classified according to their clinical presentation and histopathological pattern.

While the clinical presentation of scarring alopecia may sometimes be non-specific and misleading, in our experience the vertical histological examination of biopsies taken from active lesions allows a precise diagnosis in the vast majority of cases (Figure 2). Diagnosis follows a stepwise approach from scanning to medium- and high power magnifications. On one hand vertical in contrast to horizontal technique allows to recognize on scanning magnification dermatologic disorders which mainly affect the interfollicular epidermis. These occur more commonly on non-hairy skin, but just by chance are seen in hairy areas, too or exclusively, such as eczema or psoriasis, to mention the most classic dermatoses. Furthermore, LPP/FFA is a superficial lichenoid disease and as such is best differentiated from lupus erythematosus and lichen sclerosus et atrophicus when the interfollicular epidermis is available for study. On the other hand identifying the level of disease with scanning magnification is especially helpful to evaluate deeper located inflammatory diseases such as alopecia areata. So, in a vertical section not only a "swarm of bees" around follicular papillae is diagnostic of active/full-blown stage of alopecia areata, but also a foreign-body granuloma to released hair-shaft material in circumscribed subcutaneous location which may obscure and complicate early peracute lymphocytic peribulbitis or some rare late stage of alopecia areata.

At intermediate magnification vertical sectioning allows to investigate epithelial (spongiosis, acantholysis, ballooning, interface) and stromal changes (granulation tissue, granulomas, scarring, mucin, fibrosis, sclerosis). The presence of prominent dermal mucin in lupus erythematosus and the location of subepidermal reduction of elastic fibers in lichen sclerosus et atrophicus are further helpful criteria for differential diagnosis.

Finally, at high power magnification the type of inflammatory cell involved should be investigated (lymphocytes, macrophages, neutrophils, plasma cells, fibrocytes, dendritic cells) in case supplemented by special stains for fungi, spirochetes, other bacteria and herpes virus to rule out infectious disease processes. Direct immunofluorescence and additional laboratory tests (KOH examination for fungi, cultures, ANA, TPHA, etc.) may be helpful to come to a definite diagnosis [1,2,11,15-17].

Studying vertical sections in LPP/FFA one has to be aware that not all criteria listed below are met in one slice. Therefore at times the method of horizontal sections may be a valid complement, especially in non-scarring variants of alopecia [17-20]. They enable the histopathologist to investigate more follicles, which may be in different stages of disease, in one plane. However, good laboratory handling & practice as well as medical experience with these techniques are essential. Therefore, in our opinion, when only one biopsy in - clinically scarring - alopecia is available and LPP versus lupus erythematosus is the differential diagnosis, a vertical work-up of the biopsy should be performed.

Reviewing 47 biopsies of LPP/FFA, we found the following criteria and clues in vertical sectioning especially helpful for an accurate diagnosis of this disease, many of them confirming findings of previous studies [1,2,4,7,8,11,12,15-17,21,22]. Notably, most of our specimens represent advanced stages of disease stressing the need to establish the correct diagnosis as early as possible.

**Early (n=5; all females)**

Signs similar to classic lichen planus, such as lichenoid peri-infundibular lymphocytic inflammation ("hugging type" [22]), reactive epidermal and infundibular hyperplasia (Figure 2A). The inflammatory infiltrate can sometimes involve the deep reticular dermis and thus simulate other more deeply located dermatoses especially lupus erythematosus. Further signs are basal cell vacuolization, necrotic keratocytes or apoptoses (so-called cytoid or Civatte bodies), wedge-shaped hypergranulosis and superficial pigment incontinence.

![Figure 2: Histology of LPP in different stages of the disease (H&E).](image)

**A. Early LPP.** There is infundibular hyperplasia, wedge-shaped hypergranulosis and a dense perifollicular ("hugging type") lichenoid infiltrate composed mainly of lymphocytes with little pigment incontinence and mild fibrosis.

**B. Fully developed LPP.** Infundibular hyperplasia and follicular plugging accompanied by a dense lichenoid infiltrate of lymphocytes, pigment incontinence and necrotic keratocytes/apoptoses ("cytoid or Civatte bodies").

**C. Fully developed LPP.** Perifollicular fibrosis and residual inflammation that "backs away" from the follicle.

**D. Late LPP.** Infundibular hyperplasia with wedge-shaped, superficial perifollicular fibrosis and alopecia.

**E. Late LPP.** There is a residual lymphocytic inflammatory infiltrate with pigment incontinence, dilated capillaries (indicator of - previous - inflammatory process) and fibrosis in the superficial dermis.

**F. Late LPP.** Infundibular hyperplasia with compact orthohyperkeratosis, hypergranulosis and infundibular tufts (compound follicles) accompanied by superficial scarring, subepidermal clefts and a lymphocytic inflammatory infiltrate.

**G. Late LPP.** Beneath an unremarkable epidermis there is superficial fibrosis with residual lymphocytic inflammation and telangiectasia.

**H. Late LPP.** Infundibular tufts (compound follicles) are evident. Note that the fusion occurs at the level of the infundibulum. There is mild perifollicular fibrosis.
Fully developed (n=30; 23 females, 7 males)

Follicular plugging, presence of a superficial perivascular lymphocytic inflammation with pigment incontinence, clefts between epithelium and dermis. Loss of sebaceous glands and stem cells (in case verified with anti-CK15 [23,24]), initial fibrosis (Figure 2B and 2C).

Late (n=11; 10 females, 1 male)

Thinning of follicular epithelium, peri-infundibular, superficial scar embracing the infundibulum accompanied by perifollicular mucin and wedge-shaped loss of elastic tissue, scant lymphocytic inflammation that "backs away" [16] from the follicle, infundibular tufts/follicular fusion (compound follicles) due to mild scarring around hair follicles and their infundibula in particular (which is in contrast to tufted folliculitis or folliculitis decalvans where a much more destructive and granulomatous scarring reaction accompanied by neutrophils is seen). Marked reduction of hairs and arrector pili muscles. Sometimes a moderate and superficial stromal foreign-body reaction to released hair shaft material (Figures 2D-2H).

'Burnout' (n=1; female)

Fibrous tracts in the reticular dermis mirroring the destroyed hair follicle.

In addition, we have immunohistologically investigated 38 biopsies with MiB1 (Ki-67). In contrast to normal skin and early stages of disease (n=5) we found an epithelial reduction of Ki-67 next to the inflammatory process especially in fully developed (n=6 of 22) and late stages of disease (n=9 of 11) (Figures 3A-3D). This is in part likely due to the destruction of hair follicles, especially the bulge region [12], where the follicular stem cells reside, but is similarly also observed in lichen planus without hair follicle involvement (own unpublished observations). In H&E sections of LP, LPP or FFA this is reflected by a reduction of epithelial mitoses (no more than 1 in a 4 mm punch biopsy) especially in late stages of disease. This phenomenon can only be appreciated in a vertical section and is in contrast to other lichenoid dermatoses, eczema and psoriasis (own unpublished data).

In conclusion, histopathology of scarring alopecia is a challenging
field in dermatopathology and regularly requires clinicopathological correlation. In our opinion, a vertical section is mandatory in the investigation of scarring alopecia, especially to establish the correct diagnosis of LPP / FFA.

References