

Observation of Follicular Morphology of Alopecia Areata by the Duration of the Lesion

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Students of alopecia areata (AA) face confusion in the understanding of the follicular status of the lesion. This confusion partly is related to varying histopathological descriptions given by different authors. In an attempt to clarify these varying descriptions, we made our own observations on 45 scalp biopsies from the patients with AA. The lesions were divided into four groups by the duration of the alopecia. The results were as in the following.

Initial stage (within 2 weeks after the onset, 5 cases) showed mostly the catagen stage of terminal hair follicles and pigmentary incontinence in all cases. Only 2 cases (40%) showed significant cellular infiltrate. Progressive stage (between 2 weeks and several months after onset, 11 cases) showed catagen follicles of terminal hair with the development of miniature follicles among them. Pigmentary incontinence and inflammatory cell infiltrate were seen in 9 cases (82%) and 8 cases (73%) respectively. In established stage (26 cases), miniature follicles were predominant with pigmentary incontinence (73%:19 cases) and cellular infiltrate (69%:18 cases). In recovery stage, there were normal anagen follicles with absent or decreased inflammatory cells and pigmentary incontinence. A proposal that hair follicles better be designated not only with their stages but also with their types is presented. (*Ann Dermatol* 3:(1) 23-31, 1991)

Key Words: Follicular morphology, Duration of alopecia areata.

The human hair follicle is one of the most complicated structures of the body and every hair follicle undergoes a life cycle composed of anagen, catagen and telogen stages. Because of the dynamic nature of the hair follicle development it is often difficult to determine the precise stage of the hair follicle in histologic sections. In AA the appearance of immature follicles makes this analysis even more complicated.

Adding further complexity to the histopathology of AA are the different histopathological descriptions provided by different authors. For example, in the early stage of AA, the dominant hair follicles are said to be late anagens or early catagens according to Akerman and Ragaz¹.

Lever's textbook stated that early anagen hair follicles are dominant in recent onset of AA². In the study by Messenger et al, biopsies taken early in the course of the disease showed that the majority of follicles were in telogen or late catagen and that some of the anagen bulbs were located at a higher level in the dermis than normal³. Swanson et al described the follicle of recent onset alopecia as acute involutional changes in anagen follicles⁴.

These discrepancies among the authors are believed to be due to differences in the timing of the biopsies even though all of those histopathological studies were said to be done alike during the early stage of AA. (Table 1).

We feel that the period of so-called early stage or recent onset AA is a vague designation and is decided arbitrarily by the authors. And because of the rapidly changing dynamics of the hair follicle, which are modified by the pathological impulse, the morphological findings can be quite

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Table 1. Follicular status of early stage of alopecia areata by different authors.

Ackerman ¹	(1984) : Late catagen, early catagen
Lever ²	(1983) : Early dystrophic anagen
Messenger ³	(1986) : Telogen, late catagen, higher level anagen
Swanson ⁴	(1981) : Acute involuntary changes in anagen follicles

Table 2. Follicular status of established stage of alopecia areata by different authors

Ackerman ¹	(1984) : Catagen or telogen, few or no anagen
Lever ²	(1983) : Dystrophic telogen
Messenger ³	(1986) : Smaller anagen
Swanson ⁴	(1981) : Total telogen transformation
Van Scott ⁹	(1958) : Early anagen

Table 3. Microscopical features of initial stage of AA.

Patient No.	Age	Sex	Dominant Follicles	Inflammatory cell Infiltration	Pigment Clumps
1	6	M	Catagen	+	+
2	34	M	Catagen	+	+
3	23	F	Catagen, *FDA	-	+
4	27	F	Catagen, @Mini	-	+
5	17	F	Catagen	-	+

Catagen: Catagen stage of terminal hair follicles.

* : Fully developed anagen of terminal hair follicles.

@: Miniature follicles.

different each other by the exact time of the biopsy even though they are all called alike early stage or recent onset. The similar problem can occur also in so-called fully developed stage and late stage. For example, Messenger *et al*³ described "smaller anagens" were dominant in the established stage of AA but Ackerman described that catagen or telogen follicles were dominant with few or no anagen in the fully developed lesion of AA. (Table 2)

In the hope of elucidating different reports in the histopathology of AA, we accomplished the present study.

MATERIALS AND METHODS

Scalp biopsies were taken from 45 patients with AA. They were divided arbitrarily into four groups: initial stage (5 cases), progressive stage (11 cases), established stage (26 cases) and recovery

stage (3 cases). Cases within two weeks after the onset were grouped as initial stage. Progressive stage included the cases between two weeks and several months after the onset. Established stages were referring the cases with no further development of alopecia at the time of examination. "The onset" here means initiation of symptoms in the specific bald patch where biopsy was taken. It may or may not coincide with the onset of symptom of the patient. Both the initial stage and progressive stage usually showed areas of exclamation-point hairs with apparent thinning of hairs, where biopsy specimens were taken. In established stage, the biopsy sites usually showed fine vellus type or somewhat thicker intermediate type hairs. All biopsies were sectioned serially in a vertical plane. In addition to the changes of hair follicle per se, peribulbar inflammatory cell infiltrates and peribulbar pigment clumps were observed. Only when the amounts

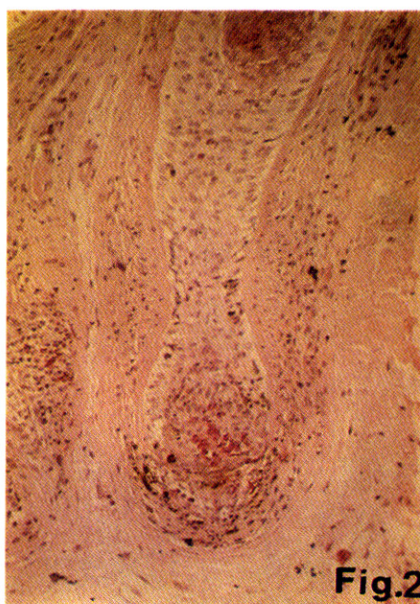


Fig. 1. Catagen stages of terminal hair follicles are prominent in initial stage of AA. (H-E stain, ×20).

Fig. 2. Higher power view of Fig. 1 showing contracting bulbar area with pigmentary incontinence and mild cellular infiltrates. The picture is thought as acute involutionary stage of anagen or very early stage of catagen (H-E stain, ×20).

Fig. 3. Another initial stage of AA showing more advanced stage of catagens compared to Fig. 1. (H-E stain, ×100).

Table 4. Microscopical features of the progressive stage of AA

Patient No.	Age	Sex	Dominant Follicles	Inflammatory cell Infiltration	Pigment Clumps
1	51	M	Catagen, #Inter, @Mini	+	+
2	20	F	Mini, Catagen	+	+
3	20	F	Mini, Inter, Catagen	+	+
4	7	F	Catagen, Mini	—	—
5	53	F	Catagen	+	+
6	50	F	Catagen	—	—
7	23	M	*FDA, Mini, Catagen	+	+
8	23	M	Catagen	+	+
9	48	F	Catagen, Mini	+	+
10	46	F	Catagen	+	+
11	19	M	Catagen	—	+

Catagen: Catagen stage of terminal hair follicles.

: Intermediated sized follicles.

@: Miniature Follicles.

* : Fully developed anagen of terminal hair follicles.

of inflammatory cell infiltrates and pigment clumps were considerable they were regarded as being present.

RESULTS

Biopsies from the initial stage of AA.

Five patients were included in this group. Histopathologic findings are summarized in Table 3 with the results.

Table 5. Microscopical features of established stage of AA.

Patient No.	Age	Sex	Dominant Follicles	Inflammatory cell Infiltration	Pigment Clumps
1	10	F	@Mini	+	-
2	20	F	#Inter, Catagen	-	+
3	10	F	Mini	-	+
4	20	F	Inter	-	+
5	19	M	Mini, Catagen	+	+
6	19	M	Mini	+	+
7	26	F	Telogen	-	-
8	12	F	Mini	+	-
9	8	M	Mini	+	-
10	46	M	Mini	+	+
11	8	M	Mini	+	+
12	17	M	Mini	+	+
13	17	M	Mini	+	+
14	22	M	Inter	+	+
15	58	F	Inter	+	+
16	34	M	Inter	-	+
17	33	M	Mini, Catagen	-	-
18	31	M	Telogen	-	-
19	21	F	Mini	+	+
20	32	F	Mini	+	+
21	25	M	Mini	+	+
22	9	M	Mini	+	-
23	19	F	*FDA, Mini	-	+
24	18	M	Mini	+	+
25	18	M	Mini	+	+
26	18	M	Inter	+	+

Catagen (telogen): Catagen (telogen) stage of terminal hair follicles.

@: Miniature follicles.

: Intermediate sized follicles.

* : Fully developed anagen of terminal hair follicles.

Table 6. Microscopical features of recovery stage of AA.

Patient No.	Age	Sex	Dominant Follicles	Inflammatory cell Infiltration	Pigment Clumps
1	44	F	*FDA	-	-
2	32	F	FDA, Catagen	-	-
3	43	F	FDA, @Mini, Catagen	-	+

Catagen: Catagen stage of terminal hair follicles.

* : Fully developed anagen of terminal hair follicles.

@: Miniature Follicles.

In initial stage AA, the most predominant follicles were in the catagen stages of terminal follicles in their varying stage. In three cases virtually all recognizable follicles were in the catagen stage (Fig. 1, 2, 3). In about half of the cases

peribulbar infiltrates were scant but in all cases pigment clumps were present in considerable amount. The pigment clumps were found in the fibrous tract below the follicular bulb rather than the immediate peribulbar area.

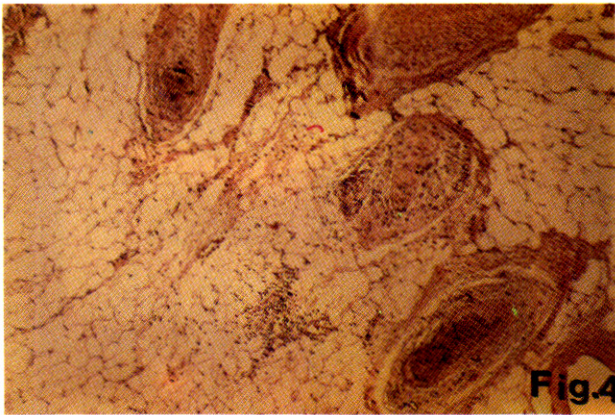
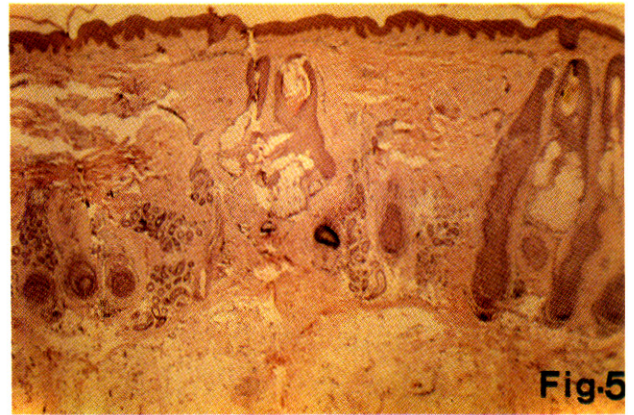
**Fig. 4****Fig. 5**

Fig. 4. Progressive stage of AA. Peribulbar infiltrates are more prominent than the initial stage. Catagen stages of terminal hair follicle are still dominant (H-E stain, ×40).

Fig. 5. In established cases, miniature follicles are prominent with peribulbar infiltrates and pigment clump. Note the level and size of the follicles compared to Fig. 1-4. They are in much higher-level and small in size (H-E stain, ×20).

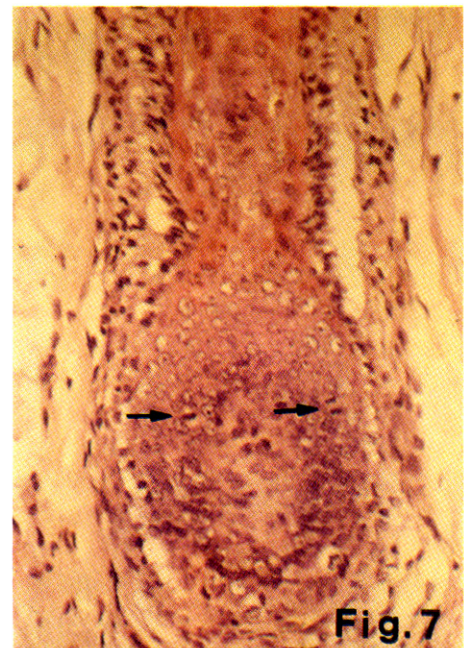
**Fig. 6****Fig. 7**

Fig. 6. Fibrous tracts (←) are also present behind the follicles having anagen activity in AA. (H-E stain, ×40).

Fig. 7. The same follicles of Fig. 6 reveals mitotic figures (←) by serial sections, which indicate the follicle is in anagen stage (H-E stain, ×400).

Biopsies from the progressive stage of AA.

Eleven patients were included in this group. Histopathologic findings are summarized in table 4.

In progressive stage, the most dominant follicles were also catagens of terminal follicles although these were less dominant compared to the initial

stage and, instead, miniature follicles appeared with some frequency. The miniature follicles were not uniform in size and in length (the depth from the surface) each other but generally they were about 2mm in length and 100 microns in width and they were believed to have trichogenic activity in general. Hair follicles which were difficult to

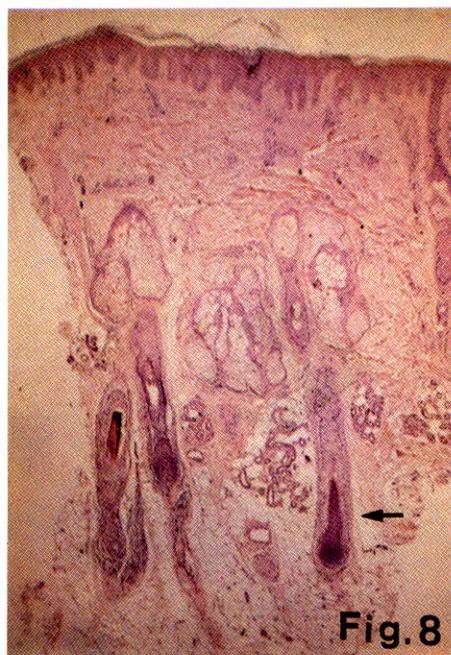


Fig. 8. A Stage V anagen follicles (←) is seen in a established stage of AA. (H-E stain, ×20).

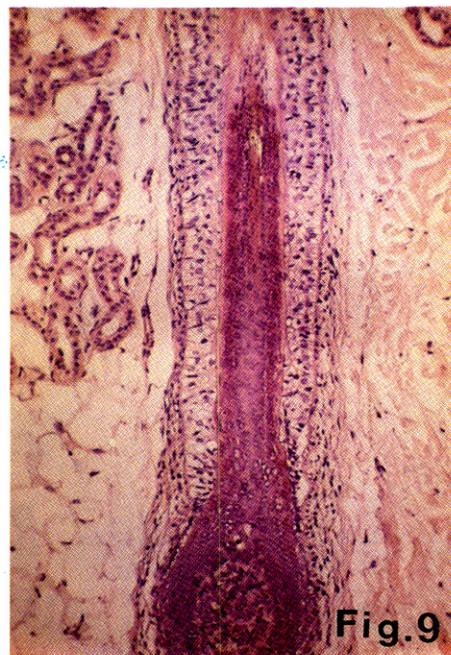


Fig. 9. Higher power of Fig. 8: Hair shaft is piercing the inner root cone, which indicate anagen stage V. (H-E stain, ×200).

be grouped into either terminal follicles or miniature follicles were classified as intermediate follicles. Clumps of melanin pigments at the peribulbar and along the inflammatory connective tissue stalks below the hair follicles were observed about as frequently as peribulbar inflammatory cell infiltrations (Fig. 4). Pigment clumps and inflammatory cell infiltrates, were present in nine (82%) and eight (73%) cases respectively.

Biopsies from the established stage of AA.

26 patients were included in this group. Histopathologic findings are summarized in Table 5.

Miniature follicles were the most dominant follicles in 15 cases. In five cases intermediate follicles were the most dominant ones. In four cases no specific follicles were dominant, but instead intermediate follicles, and terminal follicles in catagen stages or in telogen stages were present. Fully developed anagen follicles were found in only one case. Peribulbar inflammatory cells were present in 18 cases (69%) and melanin clumps in 19 cases (73%) (Fig. 5).

Biopsies from the recovery stage of AA.

Three patients were included in this group. Histopathologic findings are summarized in table 6.

The fully developed anagen stages of terminal follicles was most dominant in one case. In two cases not only the anagen terminal follicles but also miniature follicles and terminal follicles in catagen stages were frequently observed. Peribulbar inflammatory cell infiltrates were not present in all of the cases and pigment clumps were present in only one case.

DISCUSSION

Man shows different types of hairs according to the ages, races and anatomical locations of the each individual. In fetal life lanugo type hairs cover all the body surface and in perinatal life vellus type hairs replace the lanugo hairs. By the growing of the individual, terminal hairs take place on various parts of the body such as scalp and eye-brows through the intermediate hairs. The degree of changing into terminal hair follicles from

embryological follicles shows wide range of individual variations.

The growth of all types of hairs in man occurs discontinuously showing cyclic changes. The hair cycle comprises anagen: a stage of active continuous hair production, catagen: a stage of short transition, and telogen: a resting stage without hair production.

In histological sections of hair follicles, the student can recognize both of types and stages of the hair follicles. In AA, a characteristic hair type appears which does not develop normally. It is called miniature hair^{2, 5}, diminutive hair², or higher level anagen⁶. These abnormal hair follicles also show cyclic changes though the cycle is thought a truncated one.

In the tables of this paper, the catagens, telogens or anagens indicate the corresponding stages of terminal hair follicles. The miniature follicles were thought to have trichogenic activity in general by the presence of mitotic figures and/or inner root sheath cones and hence could be called anagens. But because we couldn't prove the trichogenic activity of the every miniature follicle even though we performed serial sections and to differentiate from the usual anagens of terminal hair follicle, we described it as a miniature follicle. The size of the miniature follicle is about 2mm in length and 100 micron in width while an usual anagen follicle of terminal scalp hair is longer than 3.5mm and wider than 200 micron.

From the point of follicular morphology we have observed, AA begins by formation of catagen follicles. Biopsy of the very initial stages of AA showed almost exclusively catagen follicles. We could observe various stages of catagens from the very initial one similar to anagen follicle in shape to the advanced one showing much contracted shriveled follicular epithelium.

When Messenger et al³ said that biopsies taken early in the course of the disease showed the majority of follicles in telogen or late catagen with some of higher level anagen, the period in which he did the biopsies would probably be later than the time we designated as initial stage. In Lever's textbook², it reads as follows; early anagen hair structures usually predominate in lesions of alopecia areata of recent onset. The "recent

onset" of the textbook is thought to be more later than the Messenger's "early in the course of the disease". And we think that Lever's early anagen hair structures indicate so-called miniature hairs or higher level anagen. Lever's "recent onset" alopecia seems to be actually fully-developed or established stage of AA. When Ackerman and Ragaz¹ said that in early lesions the dominant follicles were catagens and late anagens the description per se is quite consistent with our observation although the figures appeared in his textbook were different. The figures of the early lesion of alopecia areata of one of his books¹ appear to be actually showing miniature follicles or higher level anagens, which are features of an established lesion of AA. Ackerman and Ragaz¹ described that they judged the follicles as catagen because they had fibrous tracts behind the recognizable hair bulbs and papillae. But we have observed the fibrous tracts are also present behind the bulbs with anagen activity (Fig. 6), which could be proved by mitotic figures in the matrix cells (Fig. 7). To observe mitotic figures in a given hair bulb, examinations by serial sectioning were usually needed. Swanson's et al⁴ "acute involutionary changes in anagen follicles" in recent onset alopecia is believed to be the same as the initial catagen follicle we demonstrated in Fig. 2.

In established stage of AA, Messenger et al³ observed the small anagen and the telogen follicles were present with varying proportions. Mehregan⁵ mentioned miniature type follicles with trichogenic activity and solid cords of undifferentiated basaloid cells. We think that the trichogenic activity should be interpreted as anagen function. These observations of the two authors are thought to be quite consistent with the result we made even though there are some discrepancy in the frequency of telogen follicles. One of the reasons why telogen follicles were not numbered as many as Messenger observed may be that it was difficult to prove telogens against catagens or anagens when the follicle was not sectioned vertically throughout its whole length because the upper permanent part of hair follicle sheath shows the same appearance in all the three stages.

Ackerman and Ragaz¹ described that in estab-

lished lesions most hair follicles are in catagen and telogen with few or no follicle in anagen. The description is apparently different from other authors including us.

We guess that this is because they interpreted the anagens (miniature follicles with trichogenic activity) with fibrous tracts behind as catagens.

In short AA begins as formations of catagen follicles and continues as formations of abnormally small anagen follicles. The time between the beginning stage and the continuing stage can not be sharply divided so that it may be understandable that there are differences in the histopathological descriptions of AA in regard to the time of onset such as lesions of recent onset or lesions of established disease. The progressive stage we have made in this paper is thought to be simply quite vague transitional period to enter the established stage where miniature anagen follicles are dominant. The miniature⁷ follicles of AA are also thought to undergo cyclic changes even though they do not form strong anagen follicles normally seen. But because any follicle is being called anagen only if the follicle has trichogenic activity (the situation is also same in catagen, if it is in involutionary stage, and in telogen, if it is in resting stage.), we feel that simple usages of anagen, catagen and telogen give to the readers of histopathology of AA much difficulties in figuring out follicular morphology. So many authors use modifying adjectives such as small^{2, 5}, higher level⁶, or dystrophic⁷. Headington et al⁸ suggested new term, nanogen, to designate catagen-telogen in AA. We would like to clarify type of follicles when we call the stage of follicles. For example, anagen stage of terminal follicles, anagen stage of miniature follicles of AA, or anagen stage of vellus hair follicles et al would be desirable.

Messenger et al³ advocated that in AA hair growth halt in anagen stage III rather than anagen stage IV as Van Scott⁹ stated. We observed anagen stage V follicles in the established lesions of AA as shown in Fig. 8, 9. But whether it is anagen stage III or anagen stage V which is halted in AA, the more important point we believe is that the halted anagen stage III (or V) is not the same as anagen stage III (or V) of normal terminal

follicle.

The cause of these follicular changes is not revealed yet. The studies about peribulbar lymphocytic infiltrates¹⁰, alterations of subsets of peripheral blood lymphocytes and circulating antibodies to thyroid antigens¹¹ have continued. But it is not known yet if the primary abnormality in AA is in the hair follicle to which lymphocytes are then attracted, or if the primary abnormality is in the lymphocytes themselves.

We have observed appreciable inflammatory cell infiltrates in 2 cases (40%) among the 5 cases of AA in which biopsies were done in initial stage. The incidence of inflammatory cell infiltrations were higher in progressive or established stage. But melanin pigment clumps located at the infarbulbar or peribulbar areas were present in all cases of initial stage lesions and about 70% of progressive or established cases. We understand what Muller described this way that the amount of melanin present in the papilla and surrounding tissues was always slight to moderate and seen in 27% of the patients (of trichotillomania) but was intense in alopecia areata.¹² Clinically it is well known that senile white hairs are less susceptible to the disease. With this clinical experience the proposals that pigmentary mechanisms in the hair bulb are of primary importance in the pathogenesis of AA seem to deserve to be considered.^{13, 14, 15}

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