Aplasia cutis congenita of the scalp: Histopathologic features and clinicopathologic correlation in a case series

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Abstract

Background: Aplasia cutis congenita (ACC) is a rare and heterogeneous disorder characterized by congenital absence of skin. The scalp is the most commonly affected site and lesions may overlie deeper ectodermal abnormalities. The exact etiology is still unknown, and histopathologic features are poorly defined.

Methods: A series of 10 cases from nine patients was analyzed to characterize the clinicopathologic spectrum and age-related changes of ACC of the scalp. Hematoxylin and eosin, S100, Elastica van Gieson, and Weigert elastic stains were performed, and clinical information was retrieved from archived medical files.

Results: Patient ages ranged from 1 day to 39 years (median 57 months). All cases resembled deep-reaching scars with almost complete loss of all adnexal structures. Isolated residual hair follicles were present in 8/10 and sweat glands and ducts in 2/10 cases. The subcutis was thinned or absent. Elastic fibers were always more fragmented than in normal tissue, and the thickness and density increased over time. There was no gain of adnexal structures with increasing age.

Conclusions: ACC represents a congenital scarring alopecia with permanent loss of skin appendages. Histopathologic changes resemble a deep-reaching scar with fragmented elastic fibers and differentiate ACC from all other forms of non-traumatic congenital alopecias.

Keywords
a) aplasia cutis congenita, cicatricial alopecia, congenital scalp defect, ectodermal dysplasia, elastic fibers

1 INTRODUCTION

Aplasia cutis congenita (ACC) is a rare and heterogeneous group of congenital disorders that are characterized by localized or widespread absence of skin. The reported incidence is 1 to 3 in 10,000 live births, and the exact pathogenesis is unknown. Most commonly, ACC presents as small hairless patch on the scalp vertex but can occur anywhere on the body and be associated with other abnormalities. Frieden classified ACC into nine groups depending on the occurrence of other physical anomalies or malformation syndromes. Only a few cases have been analyzed microscopically as the diagnosis usually rests with the clinician. Microscopic findings are predominantly based on single case reports, and thus, histopathologic characteristics are poorly defined, conflicting, and age-related changes unknown. Clinical differentiation of ACC from other forms of congenital alopecias can be challenging and histopathological analysis is critical in these cases.

In this study, we investigated the histopathologic spectrum of ACC with emphasis on elastic fibers and age-related changes.
2 | PATIENTS AND METHODS

Dermatopathology reports of the Department of Dermatology of the University Hospital Tübingen between 2005 and 2019 were searched for the keyword ACC. Ten cases from nine patients were identified, and clinical information were retrieved from archived medical files. All cases diagnosed as ACC were present at birth, and patient #6 had three lesions that were excised at two different time points. Formalin-fixed, paraffin-embedded tissue was cut into 2.5 to 5 μm thick sections and stained with hematoxylin and eosin (H&E), anti-S100 (dilution 1:2000, Table 1: Clinicopathologic features of 10 cases of aplasia cutis congenita of the scalp.

| Patient # | Age | Gender | Site | Elastic fibers | Adnexal structures | Epidermis | Dermal collagen | Subcutis |
|-----------|-----|--------|------|---------------|-------------------|-----------|----------------|----------|
|           |     |        |      | Grading        | Single vellus hairs | Eroded and flat | Compact | Missing |
| 1         | 1 d | F      | Vertex | Yes 1 | No sweat glands | Effacement of rete ridges | | |
| 2         | 2 mo| F      | Vertex | Yes 2 | No sweat glands | Flat | Effacement of rete ridges | Compact | Missing |
| 3         | 13 mo | M    | Vertex | Yes 2 | Single terminal hairs | Dome-shaped and thin | Compact | Missing |
| 4         | 18 mo | F    | Vertex | Yes 2 | No sweat glands | Dome-shaped and thin | Compact | n.a. |
| 5         | 4 y | F      | Vertex | Yes 2 | Single vellus hairs | Dome-shaped and thin | Compact | n.a. |
| 6         | 5 y | M      | Vertex | Yes 2 | No sweat glands | Dome-shaped and thin | Compact | Missing |
| 7         | 6 y | M      | Vertex | Yes 2 | Completely absent | Dome-shaped and thin | Compact | Missing |
| 8         | 10 y | M     | Vertex | Yes 2 | No hair follicles | Dome-shaped and thin | Compact | Thin |
| 9         | 25 y | F    | Vertex | Yes 3 | Single vellus hairs | Flat and thin | Compact | Missing |
| 10        | 39 y | F    | Left parietal | Yes 3 | Single vellus hairs | Flat | Effacement of rete ridges | Compact | Missing |

Abbreviations: f, female; m, male; n.a., not applicable.

Grading of elastic fibers: 0, no elastic fibers detected; 1, thin and focal elastic fibers; 2, thin and diffuse elastic fibers; 3, thick and diffuse elastic fibers.

Table 2: Clinical information of the nine patients.

| Patient # | No. of lesions | Clinical impression/clinical diagnosis | Clinical information |
|-----------|----------------|----------------------------------------|----------------------|
| 1         | 1              | Ulcer/ACC                              | Use of vacuum-extractor at birth
Bone defect above the superior sagittal sinus, intact dura, no cerebral malformations
Mild aortic regurgitation and left-to-right shunt through small patent foramen ovale |
| 2         | 1              | Scar/ACC                               | Unremarkable cranial imaging
No known abnormalities |
| 3         | 4              | Keloid/ACC                             | Occipital abrasion at birth
No known abnormalities |
| 4         | 1              | Hypertrophic scar/ACC                   | Unremarkable pregnancy, cranial imaging, and development
No known abnormalities |
| 5         | 1              | Hairless plaque/nevus sebaceous         | Unremarkable cranial imaging
No known abnormalities |
| 6         | 3              | Yellowish nodules/epidermal cysts       | Unremarkable cranial imaging
No known abnormalities |
| 7         | 1              | Scar/ACC                               | No known abnormalities |
| 8         | 2              | Indurated scar/ACC                      | No known abnormalities |
| 9         | 1              | Scar/morphea en coup de sabre           | Use of vacuum-extractor at birth; birth-related trauma possible
Migraine-like headache in lesional area but no known abnormalities |
catalog number Z0311, Dako), Elastica van Gieson (EVG), and Weigert elastic stain. Immunohistochemistry was performed on an automated immunostainer (Leica Bond-MAX, Leica Biosystems).

The fragmentation and density of elastic fibers within ACC were graded from 0 to 3 according to Roten et al.4: 0 = no elastic fibers detected; 1 = thin and focal elastic fibers; 2 = thin and diffuse elastic fibers; and 3 = thick and diffuse elastic fibers.

3 | RESULTS

3.1 | Clinical characteristics

Tables 1 and 2 summarize the findings of the study. Patient age at biopsy ranged from 1 day to 39 years (median 57 months) and there was a female predominance. All patients presented with circumscribed hairless areas on the scalp since birth (Figure 1A,C) and with the clinical impression of scars (6/9 patients), multiple yellowish nodules (1/9), a skin-colored plaque (1/9), or ulcer (1/9). ACC was clinically suspected in 6/9 patients whereas the remaining diagnoses included nevus sebaceus, epidermoid cyst, and morphea en coup de sabre. Cranial imaging was documented in 5/9 patients of which one patient (#1) presented with a localized bone defect beneath the affected skin. None of the patients showed further abnormalities, or had a known genodermatosis, malformation syndrome, or associated epidermolysis bullosa.

3.2 | Histopathologic characteristics

Histopathological examination demonstrated that all cases resembled scars with a complete loss of all adnexal structures (folliculosebaceous units, arrector pili muscles, sweat glands, and ducts) in one patient (#7) and near-complete loss in all other cases (Figures 1 and 2, Table 1). Scattered hair follicles were found in 8/10 cases but sweat glands and ducts were found in only 2/10 cases. Arrector pili muscles were rarely observed, and if present, they were usually associated with an adjacent hair follicle. The epidermal silhouette was either dome-shaped (6/10) or flat (4/10) and ACC showed a wedge-shaped configuration in all eight cases that also included normal surrounding tissue (Figure 2D). In 9/10 cases, dermal collagen bundles were compact, showed a more parallel orientation than in normal skin and blood vessels ran perpendicular to the epidermis (EVG stain; Figure 2F). Patient #1 demonstrated loosely arranged collagen bundles with parallel orientation and ectatic vessels (Figure 2A,). Intralesional elastic fibers were reduced, always more fragmented than in the surrounding normal tissue (Figure 3A-C) and the thickness and density increased with older age (Figure 3D-F). The subcutis was thinned in one case (#6) or replaced by collagen bundles in 7/8 evaluable cases. None of the patients had a meningocele or cephalocele, and none of the biopsies contained heterotopic brain tissue.

Dermal inflammatory infiltrates were found in the three youngest patients (#1, #2, and #3; age range 1 day to 13 months) consisting of erythrocyte extravasation with interstitial neutrophils (patient #1; Figure 2A,B), a perivascular and interstitial lymphoepithelial infiltrate (patient #2; Figure 4A) and a slight perivascular lymphocytic infiltrate (patient #3), respectively.

In addition, there were some unexpected findings: Dermal free-floating hair shafts with foreign body giant cells and milia formation were found in patient #2 (Figure 4A,B). Scar tissue did not always replace the entire dermis but also surrounded hair follicles or overlay them at the periphery of the lesion (Figure 4C,D). Irregularly arranged nerve fascicles resembled a traumatic neuroma at the deep lateral margin of the ACC in
patient #9 (Figure 4E,F). Cutaneous nerves were also identified by H&E and S100 stain in all other cases but they were not increased.

4 | DISCUSSION

The histopathologic spectrum and age-related changes of ACC are largely unknown. This study refines diagnostic criteria of ACC and identified consistent histopathologic characteristics in patients of different age. All lesions resembled deep-reaching scars with an almost complete absence of adnexal structures, but some hair follicles were preserved in most patients. The changes of the elastic fiber network and collagen bundles paralleled those of surgical scars. There was no gain of adnexal structures with increasing age, supporting the classification of ACC as a cicatricial alopecia.

The pathogenesis of ACC is still unknown, and there is no unifying concept which could explain all cases. Various theories have been proposed, including developmental abnormalities such as incomplete closure of the neural tube and embryonic fusion lines, intrauterine trauma, amniotic adhesions to fetal skin, genetic mutations, and teratogens. During the embryonic development, epidermis, appendages, and nervous system are derived from the ectoderm whereas the connective tissue of the head and cartilage of the skull are a mixture of ectodermal and mesodermal tissue. The localized disruption of ectodermal structures and the associated malformations in some patients support the concept that ACC represents a failure of ectodermal migration. On the other hand, the evidence of scar tissue overlying terminal hairs, free-floating hair shafts with milia formation, and a neuroma at the margin of the ACC suggests that exogenous causes, such as a pre- or perinatal trauma may play a role in other cases.

As ACC can be associated with deeper tissue defects and other ectodermal abnormalities, a complete physical examination should be performed in all patients with particular emphasis on ectodermal structures (hair, teeth, nails, entire skin, and central nervous system). Neuroimaging studies (ultrasonography and magnetic resonance imaging) are indicated in patients with the "hair collar sign" and large or membranous lesions of the scalp to exclude underlying bone and neurovascular anomalies. The "hair collar sign" describes a ring of long hair encircling a congenital hairless area on the scalp and is a sign of a potential neural tube defect, such as heterotopic brain tissue, encephalocele,
Membranous ACC represents a distinct ACC variant which consists of a well-demarcated round or oval flat bulla covered by a thin membrane. This membranous type is often associated with a “hair collar sign” and has been proposed as a forme fruste of a neural tube defect due to its shared clinical and histopathologic features. As a matter of precaution, imaging with ultrasonography is advisable before biopsy in all scalp lesions suspicious for ACC.

Correct diagnosis of ACC is crucial as it may be associated with other abnormalities and genetic syndromes with autosomal dominant or recessive inheritance. Clinical differentiation from other congenital alopecias can be challenging and histopathologic analysis may be necessary in these cases. Nevus sebaceus is a more common congenital lesion that occurs primarily on the scalp as a hairless plaque. It represents a benign hamartoma of the skin that combines a variety of epidermal and adnexal abnormalities. Samples of nevus sebaceus in children invariably contain primitive hair follicles and often show epidermal alterations such as acanthosis, spongiosis, and papillomatosis. Hyperplastic sebaceous glands occur later in life but ectopic apocrine glands can also be found in children. Rare differential diagnoses of focal congenital hair loss include the benign non-scarring alopecias congenital triangular alopecia and congenital alopecia areata. Congenital triangular alopecia usually affects the frontotemporal region and rarely involves the occipital scalp. Microscopically, terminal hair follicles are replaced by sparse vellus hair follicles but the number of folliculosebaceous units is usually in the normal range. Congenital alopecia areata shows miniaturized anagen follicles and lymphocytic infiltrates around the bulbs but no scarring. Scarring alopecias are exceedingly rare in newborns and young children but potential causes include linear morphea en coup de sabre and trauma. Clinically, morphea en coup de sabre commonly involves the frontoparietal area and is characterized by a linear indurated plaque, resembling the stroke of a sword. Early histopathologic changes reveal an edema in the papillary dermis and a superficial and deep perivascular and perineural lymphocytic infiltrate with admixed plasma cells. At a later stage, there is atrophy of the folliculosebaceous units and eccrine glands and replacement of the subcutis by collagen. Elastic fibers are typically preserved in all disease stages. External circumstances, such as perinatal trauma should also be considered in the differential diagnoses of ACC. Cephalohematoma and scalp injuries caused by forceps may heal with scarring and loss of skin appendages similar to ACC. However, traumatic defects present as fresh injuries at birth and are

**FIGURE 3** Elastic fibers in aplasia cutis congenita (Weigert elastic stain). A, Transition of normal (right) to lesional (left) skin in a 13-month-old patient (patient #3). Inserts refer to B and C. Original magnification 40x, Weigert elastic stain. Elastic fibers are reduced and more fragmented in lesional skin (B) compared with normal tissue (C). Original magnification 200x. D, Grade 1 = thin and focal elastic fibers in the 1-day-old patient #1. E, Grade 2 = thin and diffuse elastic fibers in the 10-year-old patient #6. F, Grade 3 = thick and diffuse elastic fibers in the 39-year-old patient #9. Original magnification 200x.
not preferentially located at the vertex. Yet, differentiation between ACC and birth trauma may be impossible in individual cases due to their overlapping histopathologic features and may only be achieved by clinicopathologic correlation. Although this case series is limited by the small size and the retrospective design, it clearly defines consistent clinicopathologic features and expands the spectrum of ACC by new histopathologic observations.

In summary, the histopathologic findings in ACC resemble a deep-reaching scar. The alteration of elastic fibers and loss of skin appendages differentiate ACC from all other forms of non-traumatic congenital alopecias.

ETHICS STATEMENT
Reviewed and approved by the ethics board of the Eberhard Karls University of Tübingen; project number 310/2019BO2.

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CONFLICT OF INTEREST
None declared.

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