ORIGINAL ARTICLE

Aplasia Cutis Congenita of the scalp: A three-case report and brief review

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ABSTRACT

Aplasia cutis congenita is a heterogeneous group of disorders in which larger or smaller areas have skin absence at birth. This process can be observed in isolation, or may be associated with other abnormalities.

We report three cases of uniquely located congenital skin aplasia on the scalp served at our center over the years; two cases with multiple injuries and another patient with a unique injury associated with the *"hair collar sign."* Its clinical, dermatoscopic, ultrasound and histopathological characteristics are analyzed according to each case.

INTRODUCTION

Aplasia Cutis Congenita (ACC), present at birth, is a relatively rare and heterogeneous group of congenital disorders characterized by generalized or localized absence of skin, and subcutaneous tissue, as well as bone in some other cases. Although this condition may manifest itself in any part of the body, the most frequent location is the scalp. Generally, it is identified as an isolated disorder. However, it may be associated with other genetic syndromes or congenital anomalies,[1] such as dystrophic epidermolysis and newborn epidermolysis bullosa (more specific and frequent). In general, the condition is commonly related to all clinical forms of inherited epidermolysis bullosa.[2-4] Oddly enough, these scalp birth injuries have caused parents to sue surgeons in the grounds of medical malpractice.[5]

Three cases observed at our center are reported: one current case and two from our pre-dermoscopic archives. Clinical, ultrasound, dermoscopic and histopathologic manifestations were reviewed according to each case.

CLINICAL CASES

Case Nº 1

This case presents a 5-year-old male patient who attended a medical appointment with his mother in 2010. The examination reveals no relevant personal or family medical history. He presents with a lesion in the occipital region of the scalp, whose size has reportedly increased. However, this is mostly related to the patient's physical development than to the actual lesional size (Fig. 1). The patient does not manifest any subjective symptoms.

Examination of the affected area shows triangular lesion located at the occipital region with one clearer margin and a somewhat pigmented central area of atrophic and scarred aspect. It constitutes an alopecic lesion with little remaining hair formed by two alopecic lesions separated by a narrow space. One lesion, which lies superiorly, is bigger and the second one, placed inferiorly, is smaller. (Fig 2)

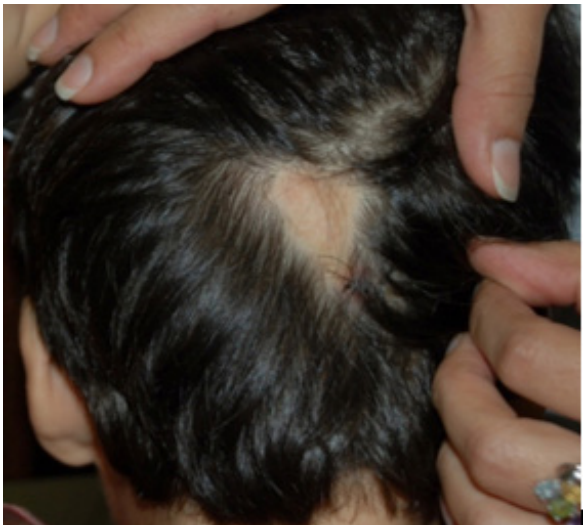

Figure 1: Alopecic lesion located at the occipital region of the scalp.

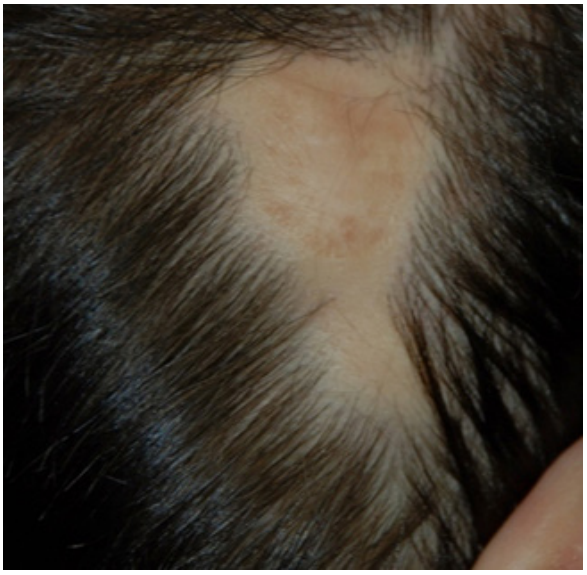

Figure 2: Close-up of previous image. Two atrophic and scarred alopecic areas divided by a narrow area.

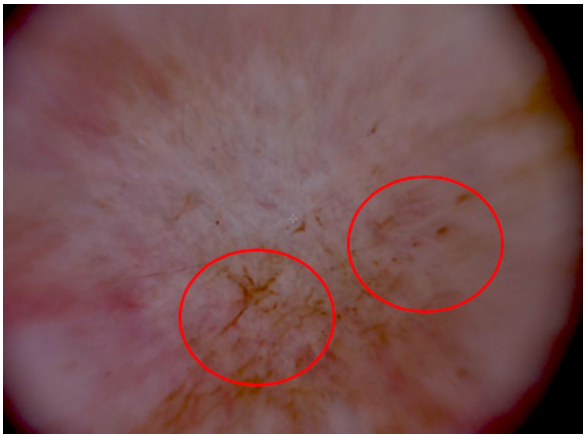

Figure 3: Lesional trichoscopy manifesting marked linear and punctiform vascular dilation and absence of follicular openings.

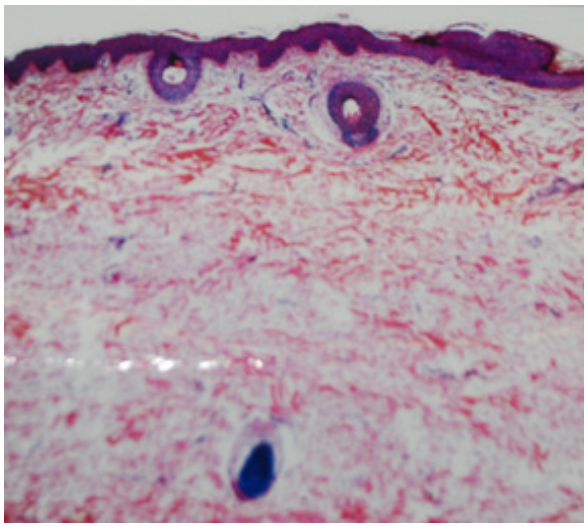

Figure 4: Absence of skin annexes. Thinning of the epidermis.

Dermoscopic examination shows total absence of follicular openings, white areas which alternate with pigmented spaces, as well as punctiform and linear dilated blood vessels shown through the epidermis. (Fig 3)

Histopathological examination reveals moderate epidermal thinning and absence of skin annexes, with the exception of rare hairy formations in the upper dermis (fig 4). Absence of significant inflammatory elements.

Case Nº 2

The case of a 7-year-old male patient with no relevant personal or family medical history is presented. The patient presents with a three-month clinical picture constituting of multiple inflamed nodules in the scalp's occipital region. Physical examination also manifests two alopecic lesions on the head, which are reportedly present since birth. Regarding the nodules, pertinent examination confirmed alopecic and aseptic nodules of the scalp as the final diagnosis.

Congenital alterations were examined; those which manifest as two rounded lesions separated by a thin bridge with little hair which, similar to the previous case, presents two areas; the first one is clearer and peripheral, and the second one is central and somewhat pigmented. Skin presents with atrophic appearance and absence of hair persistence in the affected area. (Fig. 5 and 6)

Figure 5: Two alopecic and rounded areas separated by an incomplete hairy bridge.

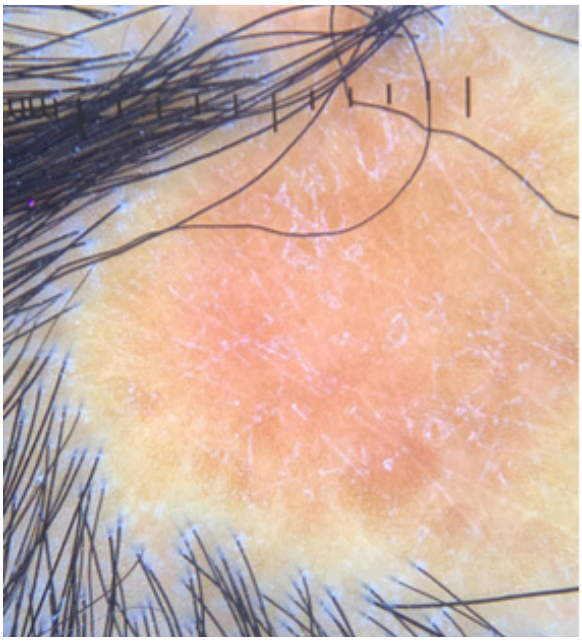

Figure 6: A close-up exhibits atrophic appearance of the skin with total absence of hair and follicular openings. A discrete erythema on the central area is observed.

A close-up of image no. 6 shows a central area exhibiting a discrete pigmented pattern and an erythematous area, visible due to a translucent epidermis which exposes the skin vascular weave.

Images 7a and 7b expose two views of the child's head and lesions; at the top, alopecic plaques representing ACC; on the back, the lesions diagnosed as alopecic and aseptic nodules of the scalp.

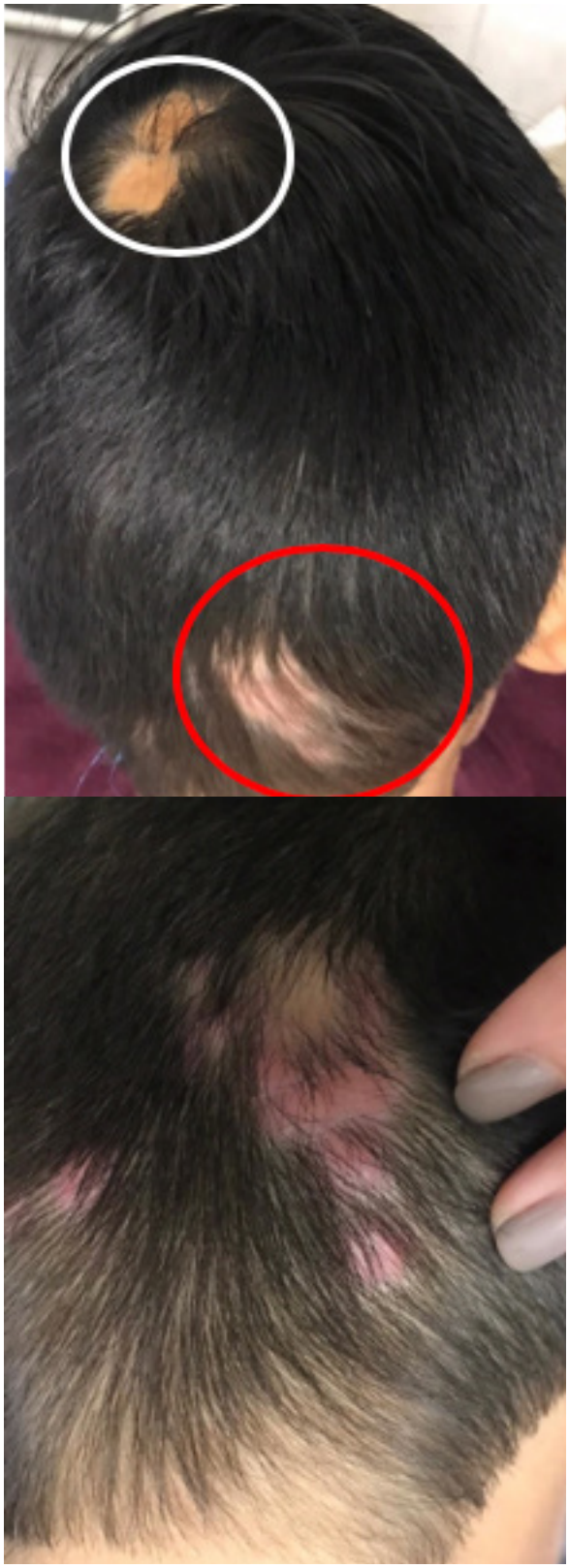

Figura 7a (superior): Círculo blanco que encierra las placas de ACC y círculo rojo que rodea la zona de los nódulos alopécicos y asépticos del CC y Figura 7b (inferior): que muestra los nódulos múltiples con mayor claridad.

A Doppler color ultrasound of the occipital region was performed with an 18 MHz high-resolution ultrasound equipment. Longitudinal view from the ultrasound reveals a dermal anechoic area of decreased thickness and increased echogenicity, suggesting dermal defect. Thickness of dermal planes and subcutaneous adjacent areas is conserved. Doppler color imaging does not detect inner or peripheral vascularization. No defects involving the bone margin are observed. (Fig 8)

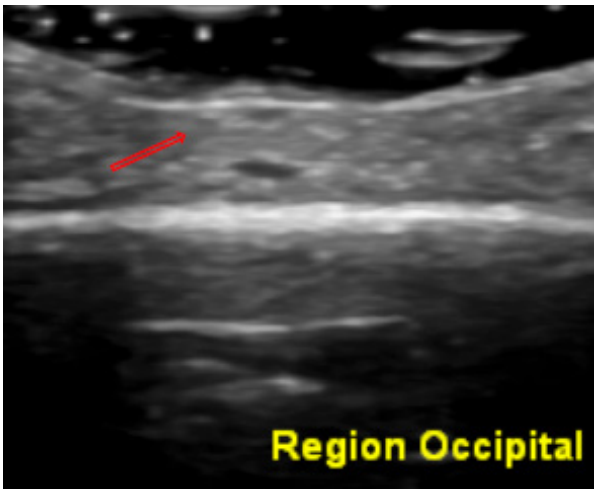

Figure 8: Ultrasound of the affected area reveals the aforementioned alterations.

Case Nº 3

A 2-month-old patient from our archives presents with scarred, irregular, erythematous, atrophic alopecic plaque present since birth. The lesion's peripheral area has a long hair collar that originates radially from the lesional margin into the outer area. No personal, family medical history, or any subjective symptoms were attributed. (Fig 9)

Membranous ACC of the scalp with *"hair collar sign"* was confirmed as the clinical diagnosis, whose close-up is featured in Fig 10. Consequently, a biopsy was performed. This revealed the presence of marked epidermal atrophy, dermal scarring fibrosis and moderate focal lymphocytic infiltration. No annexes were observed. (Fig 11)

DISCUSSION

ACC does not constitute a new clinical picture. It was first described by Cordon in 1767 while treating a patient

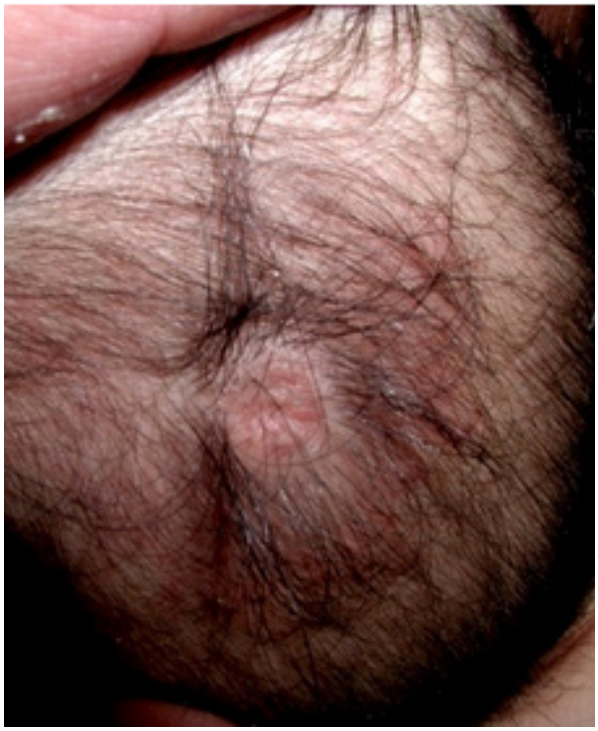

Figure 9: Occipital alopecic lesion with "hair collar sign."

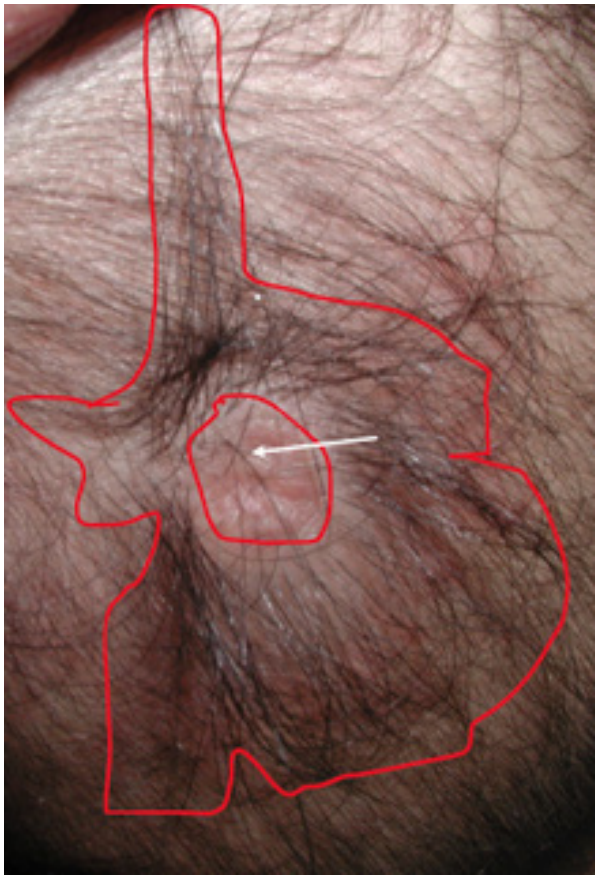

Figure 10: Outer red margin enclosing the "hair collar sign." The inner red margin demarcates the alopecic area and the white arrow highlights a few remaining hairs.

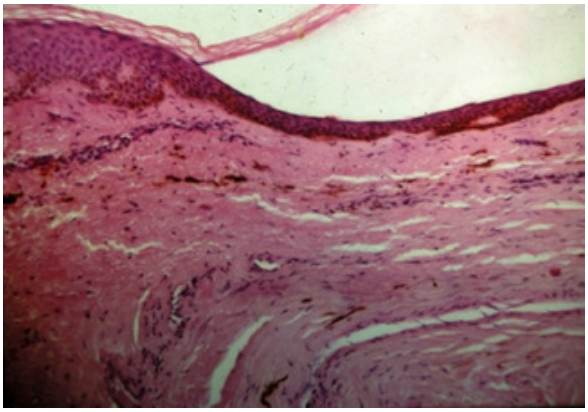

Figure 11: Microphotography exposes marked epidermal atrophy, absence of annexes and dermal scarring fibrosis with low focal lymphocytic infiltration.

presenting with ACC lesions on the lower limbs, and by Campbell in 1826, who recounted a patient manifesting the first ACC case involving the scalp.[6]

EPIDEMIOLOGY

It is a rare disorder, whose incidence rate is reported to be 1 to 3 in every 10000 births. However, it is likely that both moderate and isolated lesions are not described. In addition, solitary lesions in the context of polymalformative syndromes may not always be reported.[7] As a result, the incidence rate may not be exact. There is slight female predominance, with 85% of cases manifesting on the scalp. Most cases are sporadic. Nonetheless, family cases have been described.[8] The modes of transmission are autosomal dominant (AD) with reduced penetrance or autosomal recessive (AR).[1]

PATHOGENESIS

Etiology is not conclusive. Nevertheless, both genetic and environmental causes are discussed. Moreover, several theories have been suggested: incomplete closure of the neural tube, intrauterine trauma, uteroplacental vascular insufficiency, amniotic membrane adhesions (the amniogenic theory sustains that the amniotic membrane adheres to the fetal skin, leading to cutaneous tearing and denudation),[9] viral intrauterine infections with herpes simplex and varicella, toxoplasmosis, rubella, cytomegalovirus, TORCH syndrome infections (occurring during pregnancy) associated to ACC,[10] AIDS[11] and even syphilis (previously cited as a cause).

Several drugs taken during pregnancy, such as valproic acid, antithyroid medicine (methimazole),[12] benzodiazepines,[42] or cocaine consumption, among others, are considered as causal agents. In 2013, Marneros published a study in which he identified a well-known single gene associated to non-syndromic ACC (BMS1) in a family with a 5-generation-pedigree and AD inheritance of complete penetrance, a mutation causing a defect in the proliferation of tissues during cell development.[13-14] ACC has also been advocated as a residue of an in utero involuting hemangioma. A case of two ACC lesions of the scalp was reported on a patient suffering from intracranial malformation (encephalotrigeminal angiomatosis).[15]

CLASSIFICATION

Many classification systems have been suggested. However, only two have been properly accepted. The first classification system, suggested by Sybert VP, was featured in a 1985 article published by Pediatric Dermatol.[16] The following year, Frieden IJ presented a second classification system. Both systems are based on lesional localization (scalp lesions are separated from abdominal wall abnormalities), number of lesions, shape, inheritance and the presence or absence of other associated anomalies.[16-17]

Sybert classification divides lesions into 4 groups and 3 subgroups (Table I):

SYBERT CLASSIFICATION (1985)		
Group I	ACC limited to the scalp.	
Group II	ACC on the body and the scalp.	
	Subgroup 2 A	ACC involving the body and limb defects.
Group III	ACC on the body and the scalp.	
Group IV	ACC associated to epidermolysis bullosa.	
	Subgroup IV A	Bart syndrome

Table I: Aplasia Cutis Congenita classification (from Sybert[16])

Nonetheless, the most accepted classification is the one proposed by Frieden in 1986. Such system was featured in an article published by the Journal of the American Academy of Dermatology after a 120-publication review, which divided the disease into 9 subtypes.[18] (Table II)

SUBTYPE	FRIEDEN CLASSIFICATION (1986)	INHERITANCE
Subtype 1	ACC of the scalp without multiple anomalies.	AD or sporadic.
Subtype 2	ACC of the scalp associated to limb anomalies (Adams-Oliver Syndrome).	AD
Subtype 3	ACC of the scalp associated to epidermal and sebaceous nevus.	Sporadic.
Subtype 4	ACC (abdomen, lumbar region, etc.) overlapping embryonic malformations.	Subject to subjacent conditions.
Subtype 5	ACC associated to fetus papyraceus and placental infarction.	Sporadic.
Subtype 6	ACC associated to epidermolysis bullosa and with 2 variants: a) Focal without multiple congenital anomalies and b) Disseminated with congenital anomalies.	a) AD or AR according to the type of EA. b) AR
Subtype 7	ACC without blistering, located on the limbs.	AD or AR
Subtype 8	ACC caused by specific teratogens with involvement of the lower limbs.	Non-hereditary
Subtype 9	ACC associated to malformative syndromes.	It varies according to the syndrome.

Table II: Aplasia Cutis Congenita classification (from Frieden[18])

This classification has been modified to molecular and genetic diagnosis.[10-19] The following list from this modified classification corresponds to the 1st group concerning our cases. This modified classification shows the non-syndromic mode to be associated to genetic defects (gene BMS1). (Table III)

CLINICAL PICTURE OF ACC OF THE SCALP

This case, present since birth, manifests varied features which are subject to the time of occurrence, tissue involvement and grade of uterine healing.[18] As previously cited, the most common clinical manifestation is Frieden's subtype 1. Moreover, given that our three cases identify with the aforementioned subtype, a specific reference is indicated as follows:

Primarily, subtype 1 manifests as a small alopecic solitary defect located on the vertex of the scalp, covered by atrophic tissue or crust. However, small and clustered multiple lesions are rarely described. 75% of cases represent a single lesion, 20% equals two lesions and 8% corresponds to three.[10] Small lesions measuring 1 to 3 cm in diameter are commonly reported. The surface may present with granulation tissue, as well as erosions, ulcers and blisters. Subsequent to the lesional healing process, scarred scleroatrophic surface is frequently observed. At the same time, non-membranous ACC bullosa may expose a hypertrophic surface[20] with persistent annexes in some lesional areas. Most common location corresponds to the vertex, which is primarily related to tensile forces and elongation exerted on the embryonic skin, along with subjacent mesenchymal tissues and rapid brain growth throughout early development occurring at weeks 10 to 15 of gestation.[21]

GROUP	TOPOGRAPHY	ASSOCIATED ANOMALIES	INHERITANCE
I: ACC (non-syndromic) of the head: IA: Scalp - Membranous or bullosa. - Hypertrophic. A- trophic.	Scalp, generally on the vertex.	Cleft lip, cleft palate, tracheoesophageal fistula, uterine and cervical duplicity, ductus arteriosus, omphalocele, polycystic kidney, mental retardation, congenital cutis marmorata,[24] supernumerary breasts, hair collar.	AD (BMS1) or sporadic.
IB. Face	Temporal area and of the cheek.		

Table III: Modified Frieden classification[10-19]

Concerning the lesional shape, it is varied: oval, round, circular with perforating, linear, rhomboid, triangular or stellate aspect.[1] ACC is rarely presented as a blister with serous content covered by a membrane, that which corresponds to membranous ACC of the scalp.[1] When the defect manifests as a scar, it results from intrauterine healing. Irregular lesions are frequently associated with bone, dural, intracranial vascular alterations and they correspond to non-membranous stellate ACC of the scalp. The parietal region, which is closest to the cowlick section, is the most affected area. Lesions of the scalp may be associated with complications, including thrombosis, seizures or hemorrhages.[22] Subtype 1, subgroup B (face) of Frieden's modified classification presents lesions at the face and some rare lesional locations, such as the eyelid, described by Gao et al.[17]

CLINICAL VARIANTS

Three variants of ACC of the scalp (subtype 1) are currently described.

1. Membranous ACC of the scalp.
2. Membranous ACC of the scalp with "hair collar sign."
3. Non-membranous or stellate ACC of the scalp.

Membranous ACC of the scalp

Equally known as ACC bullosa, it is the most frequent form of ACC of the scalp (60%). In addition, although there are family case reports, the sporadic form is the most common manifestation. Commonly, it is present at birth and exposes a cyst or blister-like aspect covered by fine and shiny skin. Frequently presented as single, it may also manifest as multiple,[23] following a linear pattern at times.[1] There are case reports of linear ACC bullosa adopting Blaschko's lines.[25] Esterly, Drolet et al. affirm this form is a variant of the aforementioned neural tube defect, concept based on histopathological studies which show great similarity with meningocele and encephalocele. The skin and nervous system derive from the ectoderm. Moreover, separation between the neuroectoderm and epithelial ectoderm is given in the course of the neural tube closure. Consequently, this chronological association may justify why skin disorders are commonly related to neural tube defects.[26-27]

Membranous ACC with the "hair collar sign"

In contrast to other forms of ACC of the scalp, membranous ACC may present with an unusual peripheral ring of long, coarse hair, known as "hair collar." It was first described in 1989 by Comments et al, and it consists of a ring of dark, uneven, long and coarse hair surrounding a nodular congenital lesion of cystic, blister-like or atrophic aspect located on the scalp.[26-28] It is believed such lesion is caused by faulty neuronal migration resulting in the creation of aberrant neural tissue. This sign has been recognized as a marker for spinal dysraphism indicating the presence of distant occult rachischisis.[29-27]

Histology reveals:

a. Flat epidermis.
b. Missing appendages.
c. Dermal melanocytosis.
d. Dermal area without collagen and elastic fibers.
e. Macrophage hyperplasia and
f. Presence of numerous horizontally oriented, hypertrophic hair follicles, emerging from the margin of the lesion.

Non-membranous, irregular or stellate ACC of the scalp

This form exposes big, irregular, angled or stellate lesions, which leave a scar-like mark as they heal that merges into areas with conserved skin appendages. This manifestation usually follows an AD inheritance pattern. An association with subjacent bone alterations is not rare.

Irregular alterations of non-membranous ACC of the scalp are clinically different from membranous ACC. Accordingly, they may have different pathogenesis. Baselga et al.[21] suggest the sclerotic surface may result from abnormal postnatal healing, whilst large, deep or membranous scars are the product of intrauterine healing. Other authors, being Stephan et al.[7], propose as primary cause the aforeknown tensile forces exerted on the embryonic skin.

ACC DIAGNOSIS[22]

1. Lab testing is normal. There are no specific tests for the condition.
2. Dermoscopy.

3. Scalp x-rays are performed in special cases.
4. Skin biopsy (non-essential, unless important histological information is required for differential diagnosis with other clinical pictures).
5. Ultrasound, MRI in case of malformations or complications.
6. Prenatal tests, suggestive of ACC.
    a. alpha-fetoprotein levels in the amniotic fluid and maternal blood.
    b. If the ultrasonography is normal, testing for positive acetylcholinesterase is required
7. Research:
    a. Medication record during pregnancy
    b. Endocrinological state of pregnant patient
    c. Associated diseases
        I. Associated to limb diseases
            - Distal limb reduction (Adams-Oliver syndrome)
            - Hypoplasia or absence of distal phalanges
            - Congenital telangiectatic cutis marmorata
            - Hemangiomas
            - Cerebral arteriovenous malformation
            - Acrochordons
            - Supernumerary nipples
            - Woolly hair
        II. Associated to:
            - Epidermal and sebaceous nevus syndrome
            - Ophthalmic or neurologic disorders
                a. Seizures
                b. Mental retardation
                c. Corneal opacities
                d. Eyelid colobomas
8. Genetic testing

ULTRASOUND

Ultrasound imaging of the epidermis and dermis reveals subtle differences and rules out subjacent bone involvement. The author of one of the few articles written on the subject suggests that the ultrasound may show anechoic areas in the dermal layer which could correlate directly with histopathological findings and represent an ultrasonographic sign indicating ACC diagnosis.[30]

DERMOSCOPY OF ACC OF THE SCALP

Regarding dermoscopy, few reports have evaluated its use in ACC. Dermoscopy has allowed for a more reliable differential diagnosis between ACC and nevus sebaceous.[31] Moreover, this method has already been included in ACC's diagnostic protocol.[32] Several authors describe radially disposed hair shafts, as well as elongated hair follicles with pigmented proximal ends shown through a translucent epidermis, the presence of severely marked vessels directly correlated with skin atrophy and the absence of follicular openings at the center of the lesion.[33]

DIFFERENTIAL DIAGNOSIS OF ACC OF THE SCALP WITH OTHER CLINICAL PICTURES, ESPECIALLY NEVUS SEBACEOUS

Congenital alopecic areas derive from many processes, especially ACC and nevus sebaceous. Shortly after birth, differential diagnosis between the two processes may not be as easy due to unspecified clinical evidence.

During the neonatal period, differential diagnosis encompasses iatrogenic wounds caused by the procedure of amniocentesis or fetal skin biopsy, along with fetal scalp electrode application and the use of forceps or vacuum during delivery. Correspondingly, ACC must be differentiated from other pathologies, such as congenital abscess of the scalp, encephalocele, meningocele and congenital dermoid cyst.[9]

During childhood, stage that is common to many patients, differential diagnosis with other variants of scarring alopecia must be made. For example, congenital triangular alopecia, the above-named nevus sebaceous and nevus psiloliparus. It should be noted that the association with these last two conditions has been reported in several studies.[34-35] Nevus psiloliparus is a mesodermal nevus, considered as a hallmark of encephalocraniocutaneous lipomatosis and defined clinically as a smooth, well-demarcated round or oval alopecic area located at the parietal or frontoparietal region. The association of ACC and nevus psiloliparus is known as didymosis aplasticopsilolipara.[36]

If dermoscopy exposes sebaceous glands manifested as shiny yellow dots, non-associated with hair follicles, diagnosis of nevus sebaceous is simple. However, nevus sebaceous' evolutionary stages may present diverse dermoscopic patterns: aggregated, clustered yellowish globules over a yellow background, brown globules, whitish-yellow lobular aspect, yellowish-gray papillary appearance, homogeneous yellow color, irregular or arborizing linear vascularization.[37] Consequently, it is essential to recognize nevus sebaceous' different dermoscopic patterns.

If dermoscopy shows total absence of skin appendages and an epidermal translucent appearance, dermoscopic diagnosis of ACC can be confirmed.[38-40] Table IV exhibits the most relevant dermoscopic differential features, which allow for differentiation between nevus sebaceous and ACC of the scalp.

This dermoscopic differentiation is exposed in Fig. 13 through dermoscopic images of patients with both conditions.

NEVO SEBÁCEO	ACC DEL CC
Puntos amarillos no asociados con folículos pilosos	Margen de la placa alopécica – Signo del collarete de pelo – Pelos engrosados y pigmentados visibles a través de la epidermis traslúcida Centro de la placa alopécica – Ausencia de aperturas foliculares – Pérdida de los apéndices cutáneos – Apariencia traslúcida – Red vascular visible que corresponde a la atrofia cutánea

Table IV: Dermoscopic features of nevus sebaceous vs. ACC of the scalp. Extracted from Damiano et al.[39]

In fact, Fig. 12 shows the difference between the dermoscopic image of 4 patients with nevus sebaceous (4 pictures at the left) and the dermoscopy of one of our patients presenting with ACC of the scalp (picture at the right).

The four images at the left represent some of the presentation forms of nevus sebaceous: the two images at

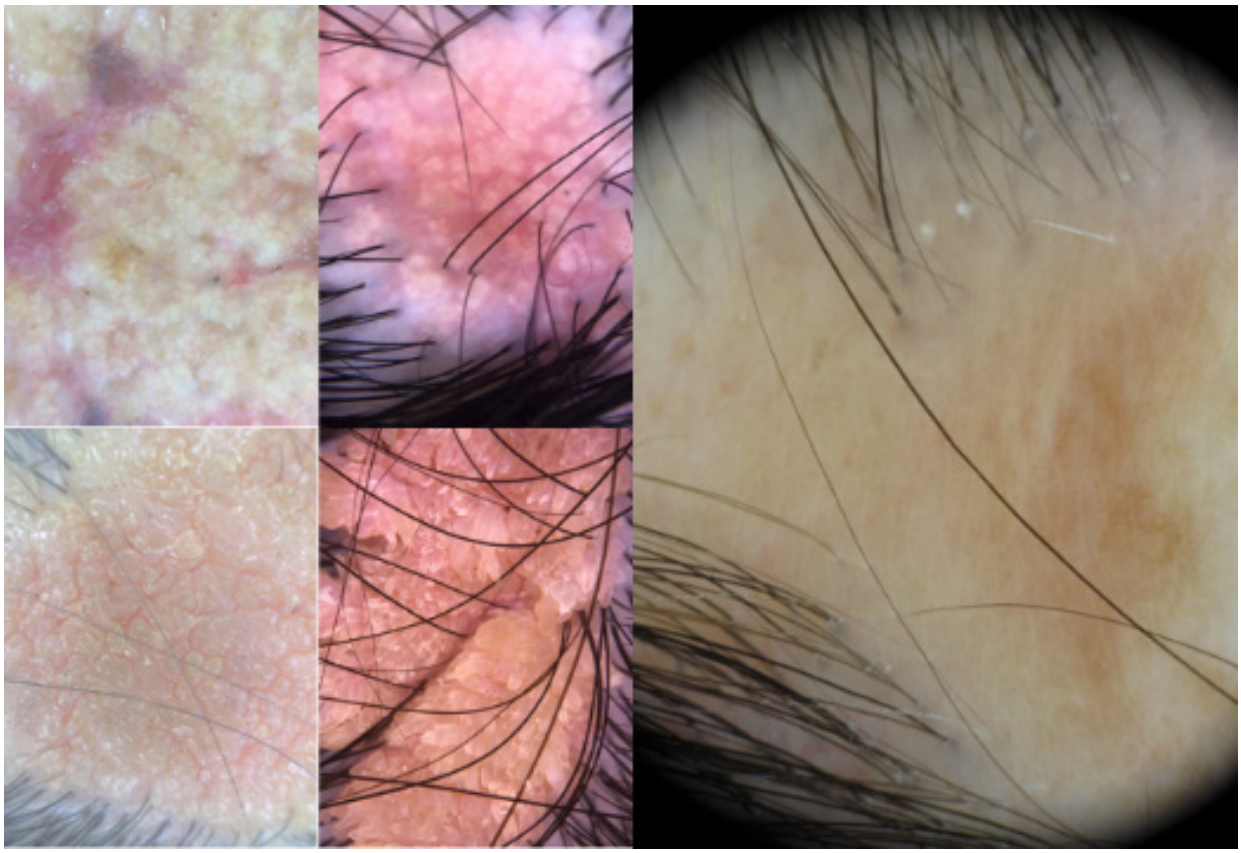

Figura 12 Imagen izquierda: dermatoscopia de 4 pacientes con nevo sebáceo de Jadassohn del CC. La imagen derecha corresponde a la dermatoscopia de un paciente con ACC del CC.

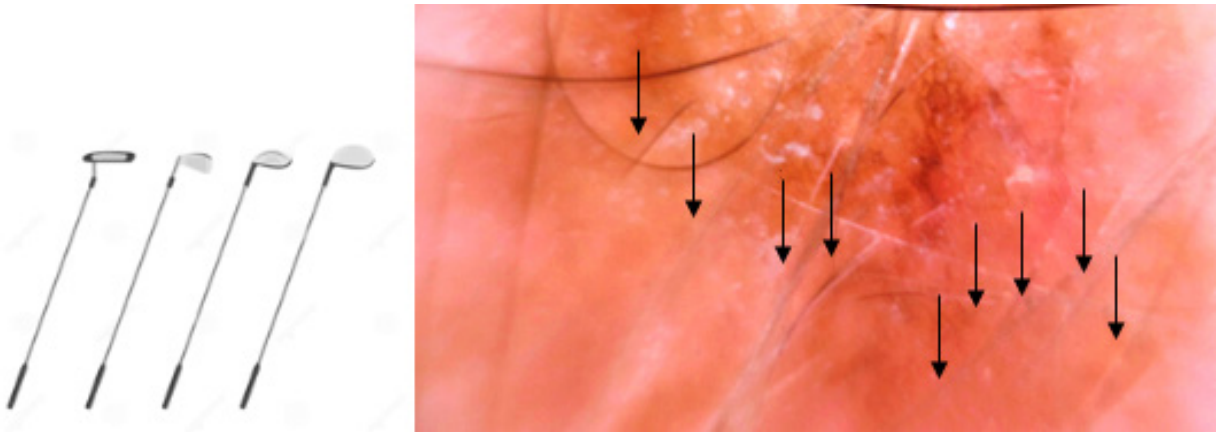

Figura 13: A la izquierda visión esquemática del "signo del set de golf" y a la derecha dermatoscopia de uno de nuestros pacientes mostrando la translucidez del CC que permite observar los bulbos (flechas negras) a través del mismo.

the top reveal the presence of clustered, aggregated yellowish globules which constitute an essential feature of nevus sebaceous; the bottom image at the left exposes a grayish-yellow papillary appearance corresponding to a verrucous alopecic elevated plaque; the bottom image at the right matches a patient with the same diagnosis manifesting a yellowish papillomatous appearance and a similar structure as the previous one. The image at the right shows total absence of follicular openings, a dermoscopic feature of ACC. Dermoscopy allows for a fairly accurate differential diagnosis between the two pathologies.

Micalli, Lacarruba y Verzi[41] conclude that the follicle peripheral orientation surrounding the alopecic area represents a diagnostic key of ACC. Such feature is recognized as "starbust hair follicles" and indicates radially oriented hair follicles shown through a thinned epidermis from the hair bulb to the follicular ostium.[41]

According to Grimalt and Cutrone, the "golf club set" sign consists of peripherally disposed hairs adopting the shape of golf clubs positioned in line under a translucent surface observed within the membranous or cystic form as a consequence of the blister's reabsorption.[42] (Fig.13). Authors suggest this must be differentiated from the aforementioned starbust sign of the membranous form of ACC described by Verzi et al.[41]

Equally, B. Lozano[43] informs that trichoscopic examination effectively rules out other entities, such as herpes simplex, epidermolysis bullosa or other trauma, because epidermal atrophy is evidenced by the hair bulbs, appreciated through its distinctive translucency. Such feature is known as the "translucency sign."

TREATMENT

Ordinarily, treatment is unnecessary, given that most cases resolve spontaneously leaving atrophic or hypertrophic (with minor occurrence) scarring. When treatment during the neonatal period is required, a conservative approach must be acknowledged through the application of topical medication to prevent infections, along with appropriate focal protection with hydrocolloid or chitosan bandages and other devices to protect potentially wounded areas. Surgical procedures are required for bigger or more profound lesions. For example, skin grafts or flaps[44-47] for definitive closure, tissue expanders, cranioplasty,[48-49] or new therapies, such as topical ozone therapy to enhance the osteogenic potential of the bone surrounding the defect.[19] Furthermore, the estimated mortality rate in patients with ACC of the scalp types 1 and 2 manifesting large defects is 14%.[47]

CONCLUSION

In accordance with what has been reviewed, it is essential that patients suffering from ACC of the scalp are properly examined to rule out congenital malformations affecting tissues and organs derived from the ectoderm, alterations which may be associated with scalp ACC type 1.

Family case research involving similar pathologies must be made in order to determine inheritance patterns.

Traditionally, ACC of the scalp, when it consists of a solitary and small lesion, does not entail any consequences. Therefore, adequate research is not usually conducted. As a consequence, changes must be made to ensure the compliance of basic research, management and follow-up protocols of the reported complications and associations.

This entity must be recognized by all physicians who work with newborns, as eventual malformations and complications may manifest and result in fatal outcomes. Diagnostic tests, such as dermoscopy and ultrasounds, are excellent tools for the diagnosis of such entity, as well as the differential diagnosis with other processes and the evaluation of potential complications.

Biopsies are generally reserved for processes involving diagnostic doubts; precise imaging procedures are employed to rule out or measure serious complications or associated clinical pictures.

Our three clinical case presentations did not include any complications or associated malformations. Moreover, their evolution matches most isolated scalp case reports.

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