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Research Article

Aplasia Cutis Congenita in Korea: Single Center Experience and Literature Review

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Abstract

Background: Aplasia Cutis Congenita (ACC) is a rare congenital malformation characterized by a localized absence of skin that most commonly affects the scalp.

Objectives: We performed the present study to elucidate the basic clinical data of ACC in Korea including demographics, clinical features, and radiologic and therapeutic results.

Methods: Fifty-nine patients (70 lesions) with ACC (35 from our department and 24 from a Koreamed database search) were enrolled. We assessed demographics, family and obstetrical histories, clinical features (multiplicity, subtype, size, shape, hair collar sign, location, and Frieden's classification), and radiologic and therapeutic results.

Results: The mean age of patients was 2.62 years, with a male to female ratio of 1.03. A minority of patients had a family history (3 patients), birth trauma (1 patient), maternal drug use (2 patients) or HIV infection (1 patient) during pregnancy, and fetus papyraceus of placental infarcts (2 patients). Six patients (6/59, 10.17%) had multiple lesions. Scarring was the most common manifestation (39/70, 55.71%). The scalp was the most commonly affected site (50 cases, 71.43%). Thirty-nine patients (66.10%) met Frieden's type I classification (scalp ACC without multiple anomalies). Radiological investigations were performed in 30 patients (30/59, 50.85%) with abnormal findings in 8 patients. Twenty-five patients (42.37%) were managed conservatively, and 17 patients (28.81%) were treated with local wound care.

Conclusion: This is the first and largest-scale study assessing the basic clinical data of ACC in Korea. The results of this study could be useful for dermatologists, pediatricians, and surgeons who routinely manage ACC.

Keywords: Aplasia cutis congenita; Congenital; Korea; Scalp; Scarring

Introduction

Aplasia Cutis Congenita (ACC) is a rare congenital skin malformation that presents as a localized skin defect [1]. It can

manifest as a cicatricial scar, ulcer or focal skin defect, and should be differentiated from encephalocele, dermoid cyst, neonatal herpes, focal dermal hypoplasia, amniotic band syndrome and nevus sebaceous [2]. To differentiate ACC from the aforementioned diagnoses, we need further clinical data on ACC including demographics, family and obstetrical histories, clinical features

such as multiplicity, size, shape, hair collar sign, location, radiologic and therapeutic results. However, most available reports on ACC are case reports or series, [3-10] and original clinical studies are rarely reported. To address this gap in the literature, we performed the current study to present the clinical data of ACC in Korea.

Materials and Methods

In this study, 59 patients (70 lesions) with ACC (35 patients from our department and 24 patients identified from a Koreamed database, medical database including all departments in Korea) were included. The patients from our department (Pusan National University Hospitals [Busan and Yangsan]) were identified retrospectively from January 2006 to August 2016. The other 24 patients with ACC were identified from a Koreamed database (<https://www.koreamed.org/>) search with the condition of “aplasia cutis congenita [title]” [11-26].

Based on medical records and clinical/radiologic images for the 35 patients from our department, or written description and clinical photos available of the 24 patients in the Koreamed search, we assessed demographics, family and obstetrical histories, clinical features (subtype, size, shape, hair collar sign, location, multiplicity, and Frieden’s classification), and radiologic and therapeutic results.

Results

Demographics and Family/Obstetric Histories

The age of patients varied between one day and 21 years (mean; 2.62 years). There were 26 newborns (44.07%; aged between 1 day and 1 month), 23 infants (38.98%; between 1 month and 3 years), 7 children (11.86%; between 4 and 17 years), and 3 adults (5.08%; between 19 and 21 years old). In total, 59 patients were enrolled (30 males, 50.85% and 29 females, 49.15%), with a male to female ratio of 1.03.

Family history of ACC was found in 3 patients (3/59, 5.08%), with mother and brother affected in 1 patient, and brothers affected in the remaining 2 patients. With respect to obstetric history, one patient had birth trauma during vaginal delivery. There were 2 patients whose mothers took methimazole during pregnancy due to their hyperthyroidism, and 1 patient whose mother was infected with Human Immunodeficiency Virus (HIV). However, there was no patient with a history of herpes simplex virus or varicella zoster virus infection during pregnancy. Two of the newborn patients were from a twin pregnancy with fetus papyraceous.

Clinical Features

Six patients (6/59, 10.17%) had multiple lesions on the scalp and extremities (1 patient - 2 lesions), trunk and extremity (1 patient - 4 lesions), localized to scalp (1 patient - 3 lesions), localized to

trunk (1 patient - 3 lesions), and localized to extremities (2 patients - 2 and 3 lesions respectively). Considering lesional multiplicity, 70 lesions were found in the 59 patients enrolled in the present study. Among the patients with multiple lesions, 4 patients had a notable obstetric history including fetus papyraceous (2 patients), Bart syndrome (1 patient), and methimazole during pregnancy (1 patient). No specific obstetric history was found in 2 patients with ACC localized to the extremities.

Clinically, ACC presented as a scarred area (cicatricial ACC, 39/70, 55.71%), ulcer (fibrinous ACC, 24/70, 34.29%) or thin membrane (membranous ACC with underlying bony defect, 7/70, 10.00%). Hypertrophic (lumpy) scar appeared in 4 lesions (4/39, 10.26%) of cicatricial type. The mean size of ACC lesions was 8.37 cm² (range, 0.09-120 cm²). The shape of ACC lesions varied and included round (29/70, 41.43%), oval (20/70, 28.57%), linear (9/70, 12.86%), polygonal (7/70, 10.00%), and stellate (5/70, 7.14%) shapes. Hair collar sign was found in 3 lesions (3/70, 4.29%). The most commonly involved site was the scalp (50/70, 71.43%), followed by the extremities (11/70, 15.71%), and trunk (9/70, 12.86%). Of the 50 scalp lesions, the vertex was the most common with (18 cases, 25.71%), followed by occipital (15/70, 21.43%), parietal (9/70, 12.86%), frontal (5/70, 7.14%), and temporal (3/70, 4.29%) areas.

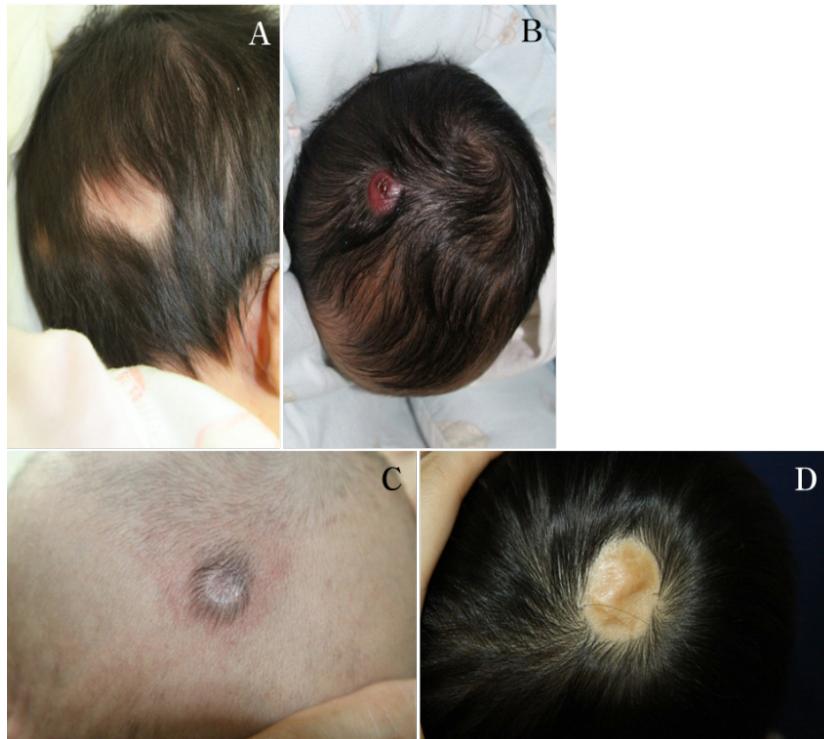
In Frieden’s classification, type I (scalp ACC without multiple anomalies) was the most common with 39 patients (39/59, 66.10%) affected, followed by type VII (ACC localized to extremities without blistering, 8/59, 13.56%), type IV (ACC overlying embryonic malformation, 4/59, 6.78%), type II (scalp ACC with associated limb abnormalities, 3/59, 5.08%), type V (ACC with associated fetus papyraceus of placental infarcts, 2/59, 3.39%), type VIII (ACC caused by specific teratogens, 2/59, 3.39%), and type VI (ACC associated with epidermolysis bullosa, 1/59, 1.69%).

Radiologic and Therapeutic Results

Radiological investigations were performed in 30 patients (30/59, 50.85%). Six patients underwent radiologic evaluation using two modalities concurrently. Standard radiography by X-ray film was performed in 14 patients (14/59, 23.73%), and this detected underlying skull defect or thinning in 3 patients (3/14, 21.43%). Ultrasound (US) was performed in 16 patients (16/59, 27.12%) by various approaches including the transfontanellar, cardiac or spinal method. Abnormal findings such as subependymal pseudocysts, dorsal dermal sinus at the sacrococcygeal junction, and cerebral palsy were observed in 3 patients (3/16, 18.75%) on US image. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) were performed in 3 patients (3/59, 5.08%), respectively. One patient exhibited an underlying skull defect on CT scan, which was previously identified on X-ray, and 1 patient

had features suggestive of cerebral palsy on MRI that were previously identified on US.

With respect to treatment, patients with ulcers (17/59, 28.81%) were treated with local wound care (dressing with topical antibiotics) which resulted in an atrophic scar. Surgical excision was performed in 9 patients (9/59, 15.25%). Hair transplantation, cranioplasty, or skin grafts were performed in 4 patients (4/59, 6.78%). Topical minoxidil was tried on 4 patients with cicatricial ACC (4/59, 6.78%) with very minimal response, and these patients subsequently underwent surgical excision or hair transplantation was done. The remaining patients (25/59, 42.37%) were managed conservatively with reassurance and follow-up. Figures 1(A-D). Tables (1 and 2)



Figures 1(A-D): Clinical features of aplasia cutis congenita (ACC). **(A)** Scar in a 2-month-old Korean female infant. **(B)** Ulcer in a 3-day-old Korean male infant. **(C)** Hair collar sign in aplasia cutis congenita in a 3-month-old Korean female infant. **(D)** Hypertrophic (lumpy) scar in a 3-year-old Korean male child.

			Present study (Koreans) (59 patients, 70 lesions, %)	Previous study [27] (Westerners) (22 patients, 22 lesions, %)
Age	Newborn		26 (44.07)	7 (31.82)
	Infant		23 (38.98)	9 (40.91)
	Child		7 (11.86)	4 (18.18)
	Adult		3 (5.08)	2 (9.09)
Sex	Male		30 (50.85)	8 (36.36)
	Female		29 (49.15)	14 (63.64)
Multiplicity			6 (10.17) - 70 lesions / 59 patients	0 (0.00) - 22 lesions / 22 patients

Subtype	Cicatricial	39 (55.71)	17 (77.27)
	Fibrinous	24 (34.29)	2 (9.09)
	Membranous	7 (10.00)	3 (13.64)
Size	≤10 cm²	60 (85.71)	16 (72.73)
	>10 cm²	10 (14.29)	6 (27.27)
Location	Scalp	50 (71.43)	16 (72.73)
	Vertex	18 (25.71)	13 (59.09)
	Occipital	15 (21.43)	0 (0.00)
	Parietal	9 (12.86)	1 (4.55)
	Frontal	5 (7.14)	2 (9.09)
	Temporal	3 (4.29)	0 (0.00)
	Trunk	9 (12.86)	5 (22.73)
	Extremity	11 (15.71)	1 (4.55)
	Round	29 (41.43)	0 (0.00)
Shape	Oval	20 (28.57)	20 (90.91)
	Linear	9 (12.86)	1 (4.55)
	Polygonal	7 (10.00)	1 (4.55)
	Stellate	5 (7.14)	0 (0.00)
	Type I	39 (66.10)	14 (63.64)
Frieden classification	Type II	3 (5.08)	2 (9.09)
	Type III	0 (0.00)	0 (0.00)
	Type IV	4 (6.78)	4 (18.18)
	Type V	2 (3.39)	0 (0.00)
	Type VI	1 (1.69)	0 (0.00)
	Type VII	8 (13.56)	1 (4.55)
	Type VIII	2 (3.39)	0 (0.00)
	Type IX	0 (0.00)	1 (4.55)
	Total	30 (50.85)	14 (63.64)
Radiologic evaluation	X-ray	14 (23.73)	4 (18.18)
	US	16 (27.12)	5 (22.73)
	CT	3 (5.08)	0 (0.00)
	MRI	3 (5.08)	7 (31.82)
	Reassurance	25 (42.37)	15 (68.18)
Treatment	Medical Dressing	17 (28.81)	5 (22.73)
	Topical minoxidil	4 (6.78)	0 (0.00)
	Surgical Excision	9 (15.25)	0 (0.00)
	Another	4 (6.78)	2 (9.09)

Table 1: Comparison between Koreans and Westerners in “Aplasia cutis congenita”.

Type I	ACC of the scalp without multiple abnormalities
Type II	ACC of the scalp with associated limb abnormalities
Type III	ACC of the scalp with associated epidermal and organoid nevi
Type IV	ACC overlying embryologic malformations
Type V	ACC associated with fetus papyraceus or placental infarcts
Type VI	ACC associated with epidermolysis bullosa
Type VII	ACC localized to the extremities without blistering and without associated abnormalities
Type VIII	ACC caused by specific teratogens
Type IX	ACC associated with malformation syndromes

Table 2: Frieden's classification of ACC [33].

Discussion

Although ACC is a rare congenital skin defect, it can involve the bone, dura mater and even sagittal venous sinus underlying the skin, [7] and can be mistaken for more serious conditions including encephaloceles, dermoid cysts, neonatal herpes, focal dermal hypoplasia, amniotic band syndrome, and nevus sebaceous [2]. Thus, further information regarding the clinical presentation of ACC is important, but data are limited, especially in Korea. Although many case reports or series have described patients with ACC, there has been only one original paper of 22 Tunisien ACC patients.

In this study, the majority of patients (49/59, 83.05%) were diagnosed with ACC as newborns and infants. Ten patients (10/59, 16.95%) were diagnosed in childhood or adulthood after visiting clinics for surgical correction of their ACC. Although the previous study conducted on Tunisien patients showed a female predominance in ACC prevalence (male to female ratio of 0.57), this study revealed a similar male to female ratio of 1.03.

Although ACC is usually sporadic, autosomal dominance and rare autosomal recessive inheritance patterns have been reported [27]. In this study, one patient exhibited autosomal dominant inheritance and two patients showed autosomal recessive pattern; in the patients with autosomal recessive inheritance, one had an affected mother and brother, and the other had an affected brother.

There was only one patient with an obstetric history of birth trauma that could be related to the genesis of ACC in our study. ACC caused by birth trauma (vacuum-extractor-related trauma) has been previously reported [28]. In another two patients, ACC was related to maternal use of methimazole during pregnancy. Various reports found that teratogens including methimazole might affect

the genesis of ACC, and those cases are classified as type VIII (ACC associated with specific teratogen) [5,16,17]. Two newborns in the present study were descended from a twin pregnancy with fetus papyraceus. Vascular compromise due to placental abnormality and thromboplastic material from fetus papyraceus is known to cause ACC type V (ACC associated with fetus papyraceous) [20,23]. One patient had a history of maternal HIV infection. ACC is also known to be related with herpes simplex virus or varicella zoster virus infection during pregnancy, but the association with HIV infection has not been reported previously [29].

In this study, 70 lesions were detected in 59 patients. Only a minority of patients (6/59, 10.17%) had multiple lesions, of which 4 also had a significant obstetric history of fetus papyraceous (2 patients), Bart syndrome (1 patient), and maternal methimazole use during pregnancy (1 patient). Taken together, these findings suggest that typical ACC (scalp ACC without other anomalies, type I) clinically manifests as a solitary lesion [11].

With respect to clinical subtype, membranous ACC was the least common presentation (7/70, 10.00%). This finding could be attributed to the fact that patients with relatively mild disease tend to present for dermatologic evaluation, and that membranous ACC itself is rare [2]. The mean size of ACC lesions was 8.37 cm² (range, 0.09 to 120 cm²), and the majority of cases (60/70, 85.71%) of ACC presented as a small hairless patch less than 10 cm². Though round or oval shape was the most common (49/70, 70.00%), as previously noted in the Tunisien study (20/22, 90.91%)²⁷, the shape of ACC lesions identified in our patient cohort varied and included linear (9/70, 12.86%), polygonal (7/70, 10.00%), and stellate (5/70, 7.14%) shapes. Hair collar sign, which can be considered as a relatively specific clinical sign of ACC, was found in only 3 lesions (3/70, 4.29%). The pathogenesis of hair collar sign is explained by the aberrant shearing forces during the development of follicles related to cranial dysraphism according to a previous report, but three cases of ACC with hair collar sign in the present study were not accompanied by cranial dysraphism [30].

ACC often presents as a solitary lesion involving the scalp, but can sometimes occur on other parts of the body [15]. The present study also showed that the scalp was the most commonly affected site (50/70, 71.43%), as demonstrated in the previous study [27]. ACC presenting as a trunk lesion is known to be associated with fetus papyraceus (death of another twin *in utero*), and tends to produce characteristic bilateral symmetrical truncal, buttock, or thigh lesions, and is caused by clots due to vascular occlusion (type V of Frieden classification)^{20,23}. Among the 7 patients with trunk lesions, 2 patients with bilateral lesions had a history of fetus papyraceous, but the remaining 5 patients with solitary lesions did not. In the case of trunk ACC, bilaterality might be the distinguishing feature of ACC that is associated with fetus papyraceous.

Frieden classified ACC into nine types according to location, other concomitant abnormalities and etiologies [12]. In present study of Korean patients, type I subset (ACC of the scalp without multiple abnormalities) was the most common (39/59, 66.10%), corresponding to the previous Tunisien reports on ACC [27]. Type II subset (Adams Oliver syndrome, ACC of the scalp with associated limb abnormalities) showed concomitant polydactyly, shortening or absence of toenails, and cutis marmorata telangiectatic congenita. Type IV subset (ACC overlying embryonic malformation) exhibited concurrent encephalocele or subependymal pseudocysts proven by imaging studies. Patients with type V (ACC with associated fetus papyraceus) lesions in the present study showed bilateral symmetrical truncal lesions corresponding to previous reports [20,23]. Type VIII (ACC caused by specific teratogens) patients in the present study had a history of methimazole exposure, which is a teratogenic drug used in the treatment of hyperthyroidism [16,17].

Radiologic evaluations such as standard radiography, US, CT or MRI could be performed to expose underlying bony abnormalities and concomitant abnormalities or malformations [31]. In the present study, underlying skull abnormalities or concomitant morbidities such as subependymal pseudocysts or cerebral palsy were detected through radiologic imaging studies. Previous reports also comment on the usefulness of radiologic studies to evaluate the extent of ACC or concurrent abnormalities [32]. Imaging studies might also help in discovering underlying concomitant lesions that might be difficult to detect by physical examination alone.

Due to the rarity of the condition, the optimal treatment method for ACC has not been established [29]. Small lesions usually heal spontaneously leaving behind an atrophic scar that tends to cause cosmetic concerns for patients [2]. In the present study, approximately one third of patients were treated with conservative therapy (dressing with topical antibiotics) to prevent secondary infection. A minority of cases received topical minoxidil to stimulate hair growth, but the results were not favorable. Surgical excision and hair transplantation also raise cosmetic concerns [21]. No severe complications such as hemorrhage, infection or mortality were reported following surgical treatment in the present study, which may be partially attributable to the fact that most of the patients enrolled had relatively mild forms of disease that did not require more invasive treatments such as skin and bone graft, flaps, tissue expansion and staged reconstruction in plastic, reconstructive and neurosurgical departments [6,9].

This study has some limitations worth noting. Although we enrolled some ACC patients from the Koreamed database, this study was effectively a single-center study. Nevertheless, we searched the database for cases of “Aplasia cutis congenita in Korea” in the title and also enrolled patients from our department

over a 10-year period, therefore ultimately enrolling a relatively large cohort of patients with ACC.

Conclusively, the present report is the first large study to describe the various clinical characteristics of Aplasia Cutis Congenita (ACC) in Korea. The present results might be useful to physicians managing ACC as part of their clinical practice, and serves as a basis for further studies on ACC.

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