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CASE SERIES

Type VII Aplasia Cutis Congenita in Neonates Related to Maternal HBV Infection? Case Report and Literature Review

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Abstract: Aplasia cutis congenita (ACC) is a rare disease with an unclear pathogenic mechanism. ACC has been suggested to result from the disrupted development or degeneration of skin in the uterus. This study describes two cases that may have underlying pathogenic cause that have not been previously reported. Two neonates who were admitted to the neonatal intensive care unit due to "skin lesions on the limbs" without other deformities or complications were diagnosed with type VII ACC by dermatologist. The mothers showed positivity for hepatitis B virus (HBV) surface antigen and elevated level of HBV DNA copies, which may be related to ACC. But this association could be a coincidence. Both neonates were treated with antibacterial dressings and achieved satisfactory healing.

Keywords: aplasia cutis congenita, case report, hepatitis B virus, newborn, skin defect

Introduction

Aplasia cutis congenita (ACC) is an uncommon disease, characterized by a localized or widespread absence of skin, that mostly affects the scalp; however, ACC has also been reported to affect the face, trunk, and/or extremities. Approximately 500 cases of ACC have been reported, and the incidence rate is approximately 3 out of every 10,000 individuals — a number that may in fact be higher due to underreporting cases.[1,2] Clinically, ACC lesions are well-demarcated ulcerated membranes, ranging from a local absence of epidermis or dermis to anomalies in subcutaneous tissue or bone. In some cases, the underlying vessels, muscles, and dura mater are exposed.[3] However, the lesion may heal in utero, presenting as scarring of the skin or patchy alopecia. Histological features of ACC vary depending on the depth of lesions. Skin structures such as hair follicles, sebaceous glands, and sweat glands are lost, in addition to a dramatic decrease in collagen fibers.[4] During the healing process, fibroblasts in the connective tissue stroma proliferate and the ulcers are flattened. Even in the case that ACC completely resolves, dermal appendages are still absent.

There are nine proposed classifications of ACC. Lesions of type I to III ACC involve the scalp. Type IV and V ACC associate with fetal abnormalities. Type VI and VII ACC affect extremities. The former is accompanied by blisters or other deformities such as absence of kidney or duodenal atresia. The latter has no associated abnormalities. Type VIII ACC is caused by specific teratogens including varicella and herpes simplex virus infection, which affect scalp or other area. Type IX ACC is associated with malformation syndrome like trisomy 13.[5]

It has been reported that ACC is associated with teratogenic drugs taken during pregnancy, such as methimazole, or intrauterine infections which are caused by herpes virus or rubella virus.[6] HBV infection during pregnancy showed an increased risk of gestational diabetes mellitus, threatened preterm labor, low weight and antepartum hemorrhage.[7] Positive serum HBV surface antigen indicates a HBV-related active status, which is associated with increased levels of proinflammatory cytokines.[8] These systemic inflammatory responses may account for some adverse outcomes of

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pregnancy.[9] However, there have been no reports of ACC cases related to maternal hepatitis B virus (HBV) infection. The present study describes two cases of ACC in neonates who had been exposed to maternal HBV infection. Patients with ACC can be managed with surgery or conservative methods depending on the size of lesions and associated complications. Our patients were treated with local wound care, each with good prognoses.

Cases Presentations

Case 1

Baby Su was born to a 30-year-old primigravida mother at 38^{+6} weeks of gestation by an elective cesarean section in a local hospital. The premature delivery was due to cephalopelvic disproportion and premature rupture of the membrane (PROM) for 11 h. Apgar scores were 10, 10, and 10 at 1, 5, and 10 min, respectively. As the skin defects on the legs were noticed at birth, the infant was transferred to the neonatal intensive care unit (NICU) of the First Affiliated Hospital of Shantou University Medical College (SUMC) soon after birth. His birth weight was 2.6 kg (5th percentile), length was 42 cm (<1st percentile), and head circumference was 30 cm (<1st percentile). Symmetrical continuous skin defects extending from the knee to the anterior tibia area, dorsal foot, and ankle with clear margins were noted on both legs, each defect with a size of $36cm^2$. There were translucent membranes covering the surfaces of the skin defects. The underlying adipose tissue, vessels, and muscles were visible, as shown in Figure 1.

No other organ abnormalities were detected in the patient according to the physical examination and ultrasound screening. The HBV surface antibody (HBsAb), core antibody (HBcAb), and e antibody (HBeAb) were positive. HBsAg, HBcAg, and HBeAg were negative. Liver enzymes were normal. Syphilis screening tests, antibodies of the human immunodeficiency virus (HIV-Ab), and IgM antibodies of herpes type 1 and type 2, rubella, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and toxoplasma were all negative.

The patient's mother had positive HBV surface antigen (HBsAg), core antigen (HBcAg), and e antigen (HBeAg). Serum HBV DNA was 3.6×10^7 IU/mL in the first trimester without any treatments. The pregnancy was otherwise uneventful. There was no similar cases or other significant family history according to his parents and grandparents.

The patient was diagnosed with ACC by dermatologist. He was given routine care. Two antibacterial ointments, sulfadiazine silver (Hengjian), and povidone iodine (Kelun) were alternately applied to the skin defects, and then covered with mildly wet dressings. The dressings were changed every other day. Normal skin began to grow over the lesions on day 30, as shown in Figure 2A. Treatment for skin lesions was stopped since then. When the patient was approximately 6-months-old, the skin defects healed without any complications, as shown in Figure 2B.

Case 2

Baby Lin presented with multiple scattered bilateral skin defects on her lower extremities for 4 days. The patient was the younger sister of the monoamniotic twins. She was born to a 30-year-old G1P1 mother at 36^{+6} wk of gestation

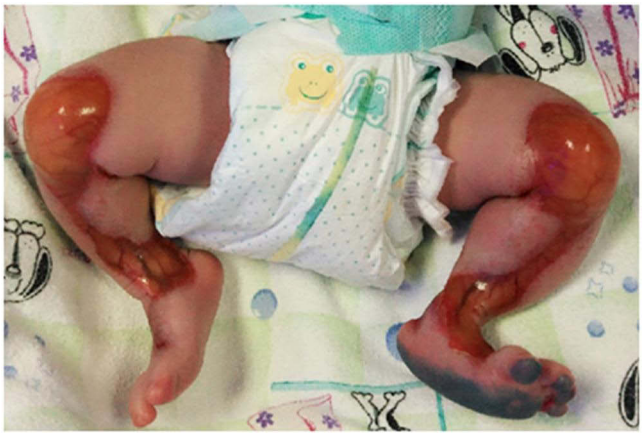

Figure 1 Aplasia cutis congenita in case 1 at birth (before treatment). Symmetric skin defects apparent in both legs. Subcutaneous fat and vessels are apparent.

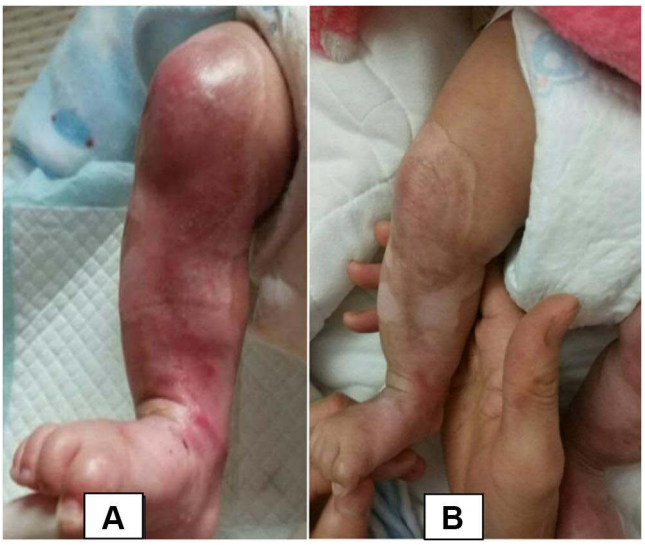

Figure 2 Aplasia cutis congenita in case 1. (**A**): At 1 mo; (**B**): At 6 mo. The skin defect healed.

by elective cesarean section due to PROM for 6 h. Apgar scores were 10 and 10 at 1 and 5 min, respectively. Her birth weight was 2.42 kg (19th percentile), length was 46 cm (29th percentile), and head circumference was 32 cm (28th percentile). Scattered fresh skin lesions were present on both legs at birth. No treatment was given until 4 days after birth, when crusting and yellow effusions developed on the surfaces of the lesions. Antibiotic ointment was applied and the patient was transferred to our NICU. Several ulcers covered by crusts and yellow effusion were noted on the anterior tibia area of both legs when she was admitted. The sizes of the skin lesions were about $10cm^2$ on the right leg and $4cm^2$ on the left leg, which are shown in Figure 3.

HBsAb, HBcAb, and HBeAb were positive. HBsAg, HBcAg, and HBeAg of the patient were negative. Syphilis screening tests, HIV-Ab, and IgM antibodies of herpes type 1 and type 2, rubella, CMV, EBV, and toxoplasma were all negative.

The patient's mother had positive serum HBsAg, HBcAg, and HBeAg. HBV DNA was 4.2×10^5 IU/mL. She did not receive any treatments. Otherwise, the maternal pregnancy was unremarkable. The patient's twin sister, was born uneventfully. There were no significant congenital abnormalities in the extended family according to his parents and grandparents.

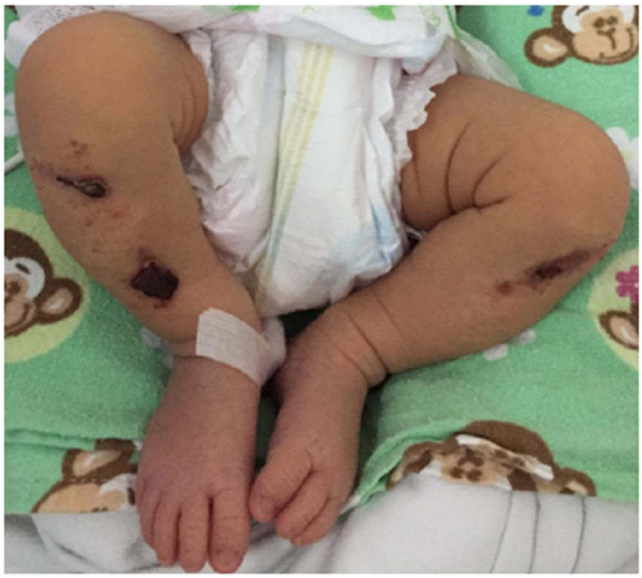

Figure 3 Aplasia cutis congenita in case 2. Skin ulcers with crusting and effusion in both legs. Several superficial crusts had been removed.

The crusts softened upon normal saline soaking and were removed. Some lesions left fresh ulcers with fundi covered by granulation tissue. The ulcers were cleaned. Mupirocin ointment (Sino-American Smithkline) topically applied and then covered with dry dressings. The dressings were changed every day until the effusion resolved. At 6 days of following treatment, several small and superficial lesions were partially healed with newly grown skin, and the patient was then discharged. One week after discharge, the parents stopped mupirocin ointment dressing when they observed that "fresh skin" had covered the lesions. Her mother refused to follow up in the outpatient clinic of SUMC due to a long distance from her home. She told the doctor over the phone that her family was satisfied because her daughters skin lesions "grow well" and left several "hardly visible scars" at 1 month after discharge.

Discussion

ACC is a rare condition that involves various skin layers. Skin lesions of type VII ACC limit on the limbs and were rarely reported compared with those involved the scalp. The etiology of ACC is unknown. Both genetic and environmental factors could contribute to its development.

The genes associated with ACC are not fully understood, some mutations have been identified in ACC cases, such as missense mutations in the ribosomal GTPase BMS1or CDC2 variat.[7,8] Notably, it has been posited that heterogeneous frame shift mutations in exons 31 and 109 of COL7A1 might be the cause of ACC with epidermolysis bullosa.[9] Different hereditary patterns have also been recognized. There was the report of the ACC occurred in the dizygotic twins.[10] Type VII ACC may be due to autosomal dominant or autosomal recessive inheritance. However, the reported cases rarely had positive family history.[11–13] Our cases could be sporadic considering negative family history and that the monozygotic twin of case 2 in our report was not affected.

The occurrence of a vascular accident in the uterus is a widely discussed hypothesis. Ischemic and thrombotic events during the fetal period disrupt normal cutaneous development and result in defects. In a patient with scalp ACC with superficial temporal artery aplasia described by Choi et al,[14] vascular disruption was considered to be the cause. This is also believed to be the cause of ACC in babies who were papyraceous fetuses or prematurity.[12,15,16] The early death of fetuses from multiple pregnancy, which usually occurs in the late first trimester or early second trimester, releases thrombotic substance, thus promoting placenta infarction, disseminated intravascular coagulation, and then cutaneous lesions. The administration of teratogenic drugs during pregnancy, such as methimazole or valproate, was thought to be the underlying cause of ACC.[6,17] Skin defects caused by intrauterine infections from the herpes virus, rubella virus, or syphilis could also present as ACC at birth.[17] Additionally, novel reproductive technologies and embryo reduction procedures may increase the risk of ACC.[18] For type VII ACC, specific pathogenic mechanism had not been reported.[11–13]

In our cases, both mothers had natural conception and did not receive any intrauterine invasive procedures. They had unremarkable pregnancy histories such as potential teratogenic drugs intake or specific organism infection, with the exception of their positivity for HBV surface antigen and high DNA replications. The patients had antibodies against HBV surface and core proteins but no evidence of active HBV infection was present. Thus, ACC did not seem to directly result from active HBV infection of the patients. Virus could be detected in 50% of occult viral infected placentas[19] and these viral-associated neonatal diseases might be due to placenta abnormalities. Studies reported that HBV X protein (HBx) plays an important role in proliferation or apoptosis of placental trophoblast cells.[20,21] Viral infection affects invasion of trophoblastic cells and modulates immune response of placenta tissue. Inappropriate trophoblastic invasion and immune response could promote dysfunction of the placenta and alter the blood flow to the fetus,[22] while interruption of blood supply to fetus is associated with ACC. As HBV biomarkers could be detected in the placenta,[23,24] another possible pathogenic mechanism could involve maternally generated antibodies to HBsAg, PreS1, or PreS2, and the corresponding antigens that form circulating complexes. These complexes could deposit in the capillaries of the placenta and cause thrombotic events that might disrupt skin development in the fetus. However, without pathological and immunological examination of the placenta, the hypothesis could not be confirmed, indicating the importance of placenta histopathological examination. Infectious and vasculopathy effects on the placenta are being increasingly recognized and reported.[25] The main histological finding of viral infected placentas is chorioamnionitis which could present as fibrinoid deposition with villous degeneration.[26] Some viri could cause thrombotic pathology in

placenta,[27] which could potentially lead to ACC. However, the relationship between HBV infection and ACC, as well as the pathogenic process of ACC, requires further investigation.

Management of ACC varies according to the size of the lesions and the general condition of the patient. As previously mentioned, lesions that occur early in pregnancy may have already healed at birth. Since ACC lesions can spontaneously heal, conservative therapy could be administered if the lesions do not involve the bones and are less than 3 cm^2. Routinely cleaning the lesions and covering them with antibiotic-impregnated dressing is a favored approach. A topical antimicrobial with near-occlusive dressing can be used to reduce the risk of infection and fluid loss.[16] At the early stage, to promote epithelialization, a wet dressing was favored and should be changed frequently enough to maintain a moist enough environment. If the wound lesions exudated, wet dressings should be changed to dry dressings.[28] According to some case reports, lesions larger than 3 cm^2 but did not affect the bone, an appropriate wound care and observation during the early days of life could reduce the need of additional surgery. Conservative therapy might provide a better outcome because surgical suturing may result in scar formation.[12,29] After several weeks to months, the lesions heal and may leave scars. During the healing period, electrolyte imbalance from epidermal water loss, nutritional deficiency from chronic blood loss, and wound pain are concerns. Attention should be paid to prevent complications such as infection and bleeding, which could be fatal. In patients with large lesions, surgery is required. Some patients may need skin allografts to promote epithelialization using local flaps or the scalp as a donor site.[30] The use of cultured keratinocytes are another approach for reconstructing skin defects. However, advanced technologies are required for their application, which are time-consuming. A combination of conservative management and secondary surgery is another option. Both of our patients were treated with antibiotic dressings and achieved satisfactory healing.

Conclusion

While congenital HBV infection might be related to ACC, these conditions may also be random associations. ACC could be conservatively managed and has a good prognosis without impacting daily life.

Institutional Review Board Statement

The Institutional Review Board of the Science and International Communication Department of Seventh Affiliated Hospital, Sun Yat-sen University provided approval for this study (IRB No. KYGJ-001-20200412-130).

Data Sharing Statement

The authors confirm that all data supporting the findings of this study are available within the article.

Patient Informed Consent

Informed consents for article publication of the case details including publication of the images were obtained from the mothers of the 2 patients.

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Disclosure

The authors report no conflicts of interest in this work.

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