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Case Report

Dermatology Section

Junctional Epidermolysis Bullosa In-utero with Pyloric Atresia and Aplasia Cutis Congenita (Carmi Syndrome): A Case Report

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ABSTRACT

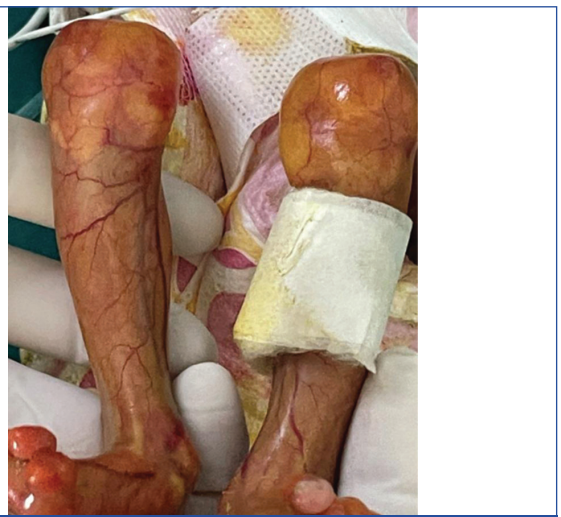
Carmi Syndrome (CS) is an extremely rare autosomal recessive genetic disorder characterised by the co-existence of Junctional Epidermolysis Bullosa (JEB), Pyloric Atresia (PA), and Aplasia Cutis Congenita (ACC). Globally, very few cases have been reported. CS is often fatal in neonates. Authors present the case of a two-day-old male preterm newborn who exhibited widespread absence of skin, especially over the lower limbs, associated with scarring skin lesions and extensive milia from birth. Other findings included bilateral microtia, nail dystrophy in the fingernails, absence of toenails, fusion of toes, corneal opacity, and a broad nasal root. Additionally, systemic involvement included PA and congenital joint contractures (arthrogryposis). The newborn was diagnosed with CS based on clinical characteristics and X-ray results. The condition was managed using a multidisciplinary approach. Unfortunately, the neonate succumbed to death on the fourth day of life due to sepsis.

Keywords: Anonychia, Arthrogryposis, Integrins, Joint contractures, Microtia, Milia, Nail dystrophy, Pseudoainhum

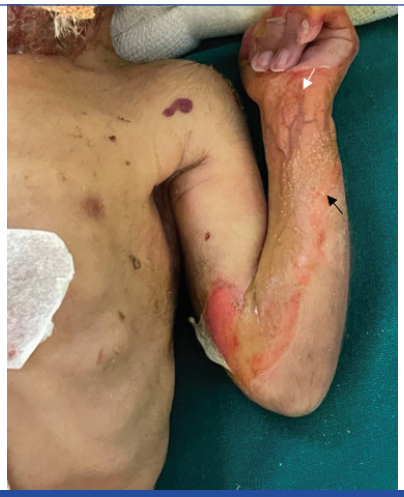
CASE REPORT

A two-day-old male preterm newborn, born at 35 weeks, was referred from the Neonatal Intensive Care Unit (NICU) with extensive congenital absence of skin, mainly over the lower extremities, and multiple scarring skin lesions since birth. He weighed 1.8 kg at delivery, had received appropriate prenatal care, and had an uneventful prenatal course. The newborn presented with fever, recurrent vomiting, and intermittent breathing difficulties. There was no consanguinity between the parents, no history of similar conditions in the family, and no history of exposure to medications or radiation during the pregnancy. His temperature was 38.7 degrees Celsius, respiratory rate 40 cycles/min, heart rate 160 beats/min, and oxygen saturation was 93% on room air.

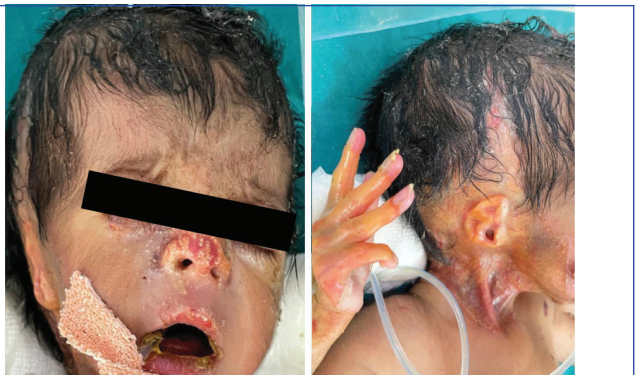
On dermatological examination, there was a total absence of skin involving the entire lower limbs [Table/Fig-1] bilaterally, including the genitalia, and localised absence of skin over the scalp, tip of the nose, anterolateral aspect of the neck (including the periauricular area), medial aspect of the forearms, and dorsum of the hands, with sharply demarcated borders. The affected areas were covered by a thin and shiny, red translucent membrane through which vascular structures were easily visible. There were multiple small areas of healed erosions of various sizes and atrophic scars with extensive milia formation over the previously described lesions as well as the uninvolved skin [Table/Fig-2,3a]. Additionally, scarring alopecia, bilateral microtia, a broad nasal root, and oral mucosal erosions were present [Table/Fig-3b].



[Table/Fig-1]: Absence of skin in both the lower limbs with easily visible vascular structures.

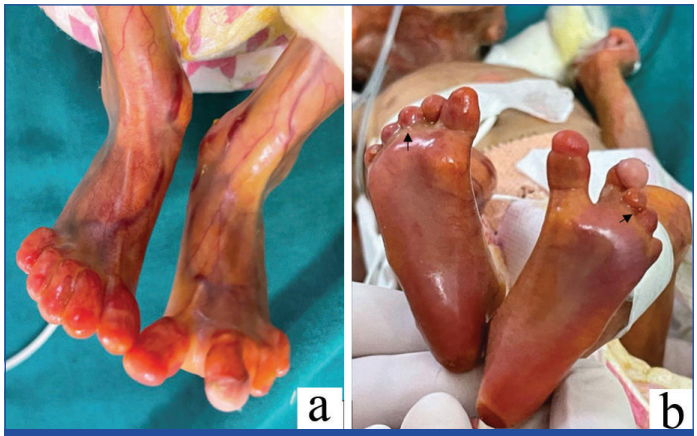


[Table/Fig-2]: Area of healed erosion with atrophic scarring and milia formation (black arrow) over pre-existing area of absent skin in the left forearm. Note the visible vascular structures (white arrow).

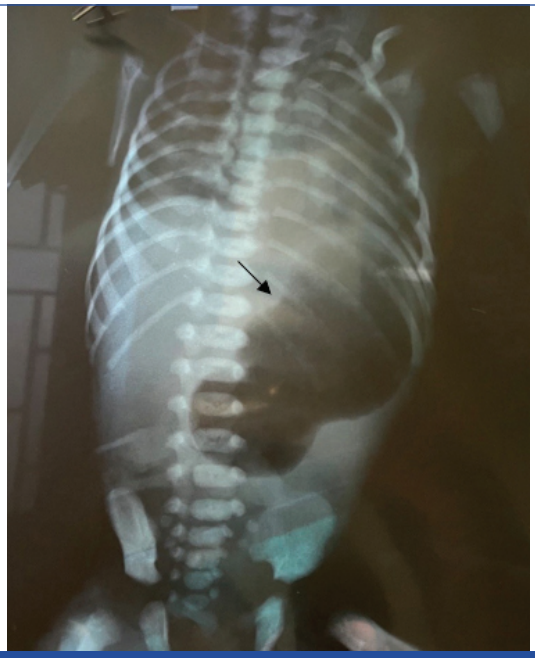


[Table/Fig-3]: a) Erosions with extensive milia formation over the nose, mouth and eyes with broad nasal root; b) Scarring alopecia in the scalp, microtia and absence of skin with erosions and milia in the neck. Nail dystrophy in the middle finger (white arrow).

The baby also had nail dystrophy in the fingernails, absence of toenails, and fusion of all toes in the right foot and the lateral four toes in the left foot (pseudosyndactyly) [Table/Fig-4a,b]. Severe joint contractures were present. Abdominal X-ray revealed a large, distended stomach with no air visible distally, suggestive of congenital PA [Table/Fig-5].



[Table/Fig-4]: a) Total absence of skin in the bilateral foot with absence of toe nails; b) Absence of skin in both soles with fusion of toes (black arrows).



[Table/Fig-5]: X-ray (Antero-posterior view) of the baby showing chest and abdomen. Black arrow showing large, distended abdomen with no air visible distally.

Based on the clinical picture, including skin lesions in the form of healed erosions and atrophic scars with excessive milia formation suggestive of junctional EB, absence of skin predominantly in the lower limbs suggestive of ACC, and associated features such as PA, microtia, severe joint contractures, nail dystrophy, anonychia, and fusion of toes, we arrived at the diagnosis of CS. Since no intact bulla was present, it was not possible to perform a skin biopsy.

Hematological reports revealed anemia (hemoglobin 9.8 g/dL), raised leukocyte count (18,000 cells/cu.mm), neutrophilia, elevated C-reactive protein (105 mg/L), and low serum glucose level (40 mg/dL). Blood cultures were positive for coagulase-negative staphylococci, while viral markers were negative. Arterial Blood Gas (ABG) analysis revealed hypokalemia and metabolic alkalosis. Instructions were given to avoid mechanical trauma.

A multi-specialty team, including a Dermatologist, Paediatrician, Paediatric surgeon, and surgical Gastroenterologist, provided comprehensive care for the newborn. Dermatological treatment included local wound care, Vaseline gauze dressing, and topical mupirocin cream application. Paediatric care involved placing the baby in a temperature-controlled incubator, correcting electrolyte disturbances, supplying oxygen through an oxygen hood, improving hydration through intravenous fluids, and administering antibiotics via an umbilical vein catheter. Despite appropriate management, the course of the disease was complicated, and the condition continued to worsen. Unfortunately, the evolution of the disease was fatal, and the newborn succumbed to severe neonatal sepsis on the fourth day of life.

DISCUSSION

The CS is a rare, fatal inherited acantholytic disease characterised by JEB and PA, often accompanied by ACC and multisystem involvement. Epidermolysis Bullosa (EB) with PA arises from mutations in the ITGA6/ITGB4 genes encoding integrins, or in the PLEC1 gene, which are essential for the formation and integrity of Hemidesmosomes (HD). There have been approximately 100 cases reported in the medical literature. A multidisciplinary approach is crucial for diagnosis and treatment.

The ACC is defined as the localised absence of skin at birth, most often occurring sporadically, although familial cases have been reported. In 85% of cases, it is typically restricted to the vertex, and limb involvement is usually bilateral, symmetrical, and not extensive unless associated with EB. The prognosis for patients with CS is poor, with a 75% mortality rate, and 50% of deaths occurring in the neonatal period.

EB is characterised by blistering of the skin and mucosal erosions caused by structural abnormalities in hemidesmosomes. There are about twenty types of congenital EB, which are classified into three groups according to the level of cleavage in the Basement Membrane Zone (BMZ): 1) EB simplex - cleavage within the basal epidermis; 2) JEB - cleavage at the lamina lucida; and 3) Dystrophic EB (DEB) - cleavage at the level of anchoring fibrils. Depending on genetic and histologic tests, JEB can be further classified as Herlitz, non-Herlitz, and JEB with PA (CS). Congenital PA caused by the absence of the $\alpha 6\beta 4$ integrin can be explained by the expression of integrin beta 4 in the gastrointestinal tract epithelium [1]. The specific type of EB can be identified through skin biopsy, electron microscopy, and immunofluorescence. Genetic analysis may assist in confirming the diagnosis.

British pathologists Swinburne LM and Kohler HG originally described CS in 1967, but the term “CS” became associated with the condition after Israeli paediatrician Rivka Carmi published a case report of two affected children in 1982, describing the association between PA and ACC- two of the main characteristics of the syndrome [2,3]. Affected newborns are often born prematurely.

The CS is characterised by skin fragility and blistering that frequently manifests at birth, along with PA. It is often fatal in early infancy. Additional characteristics include ACC, nail dystrophy, scarring alopecia, fusion of fingers and toes, ear and ocular findings, and joint abnormalities. PA is suspected when newborns experience recurrent, non-bilious vomiting and abdominal distension. Chang et al., suggested that PA is a complication of intrauterine EB, where sloughing of the pyloric mucosa leads to fibrosis and pyloric canal stenosis [1]. The treatment of PA is controversial; a series by Hayashi et al., revealed that four out of five patients with CS had long-term survival after surgery, which encouraged aggressive intervention in affected neonates [4]. However, Mylonas et al., demonstrated worse outcomes, with 49 (67.1%) of 73 patients who underwent PA repair dying postprocedure [5].

Serious complications, such as hemorrhage due to skin fragility, dehydration from fluid loss, sepsis, hypothermia, hypoglycemia, electrolyte imbalance, and shock, can lead to death. Septicaemia was the cause of death in our case. There is no definitive treatment for CS. It must be approached by a multidisciplinary team, including dermatologists, pediatricians, plastic surgeons (to correct skin defects utilising techniques such as skin grafting),

and Gastroenterologists (to determine the appropriate correction for pyloric atresia, PA). Treatment encompasses local wound care to promote epithelialisation and healing of cutaneous lesions, the use of non-adhesive dressings, control of infection, and prevention and treatment of complications. To prevent syndactyly, small bands between the fingers and toes are recommended. In cases of sepsis, intravenous antibiotic therapy is indicated. For persistent erosions that do not heal, autografts or skin allografts may be considered. Genetic counseling is essential. There are prenatal diagnostic methods for identifying JEB in utero, such as amniocentesis or chorionic villus sampling. Under the supervision of ultrasound or Foetoscopy, skin biopsies can be collected to confirm the diagnosis [6]. If a prenatal diagnosis is confirmed, a caesarean section should be considered to reduce delivery trauma.

The clinical triad of ACC, which typically manifests throughout the lower extremities, EB of any type, and nail abnormalities makes Bart syndrome a close differential diagnosis for CS. Bart et al., initially reported this uncommon entity in 1966 in 26 members of the same family across six successive generations [7]. There are some differences between CS and Bart syndrome. While CS is solely associated with JEB, Bart syndrome can be linked to any type of EB, but often to DEB. CS has an autosomal recessive inheritance pattern, while Bart syndrome follows an autosomal dominant pattern with complete penetrance. PA is definitively present in CS, but it may or may not be associated with Bart syndrome. CS requires aggressive care, whereas Bart syndrome is typically treated conservatively. Bart syndrome has a good prognosis, but CS has a poor prognosis [8]. According to a literature review conducted by Mylonas et al., 28% of individuals with CS also had Bart syndrome [5].

In the present case, the baby exhibited a typical clinical presentation, which included blistering of the skin, PA, ear deformity, congenital absence and dystrophy of nails, and congenital absence of skin throughout the lower limbs and other areas. Most of the body was covered in erosions and scars, which may have resulted in congenital contractures of the joints. According to Kanzler et al.,'s hypothesis, ACC is merely caused by in-utero EB erosions [9]. It is speculated that the healing erosions, atrophic scars, and milia development, which have been present since birth, were caused by intrauterine mechanical trauma.

CONCLUSION(S)

The present case is reported due to its rarity and associated conditions. CS in association with arthrogryposis is an unusual and highly fatal presentation. A number of clinical and laboratory factors should be considered before surgically correcting PA. The authors wish to emphasise that the majority of the skin lesions associated with JEB were found over the ACC lesions.

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