Case Series

Submitted: 06-03-2022
Accepted: 06-09-2022

DOI: https://doi.org/10.47338/jns.v11.1071

Congenital pyloric atresia with epidermolysis bullosa: A case series

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KEYWORDS

Neonate,
Gastric outlet obstruction,
Carmi syndrome,
Pyloroplasty

ABSTRACT

Background: Carmi syndrome is the name given to the association of congenital pyloric atresia and epidermolysis bullosa. It has a high mortality.

Case series: We report 3 neonates with features of multiple skin blisters and a classical X-ray picture of a single bubble appearance. Two of them underwent surgery while 1 succumbed to sepsis in the pre-operative period. One baby had delayed mortality and the other is doing well in follow-up.

Conclusions: Carmi syndrome should be kept as a differential diagnosis in neonates with skin blisters and feed intolerance. Early recognition with prompt medical and surgical management may contribute to a successful outcome.

INTRODUCTION

Congenital pyloric atresia (CPA) is a rare congenital gastrointestinal tract anomaly, with obstruction at the stomach outlet (pylorus). The CPA in the neonatal period has a classical presentation of feed intolerance, non-bilious vomiting, and upper abdominal distension, with an X-ray suggestive of a classical single bubble appearance. The late presentation has been mainly seen in the form of failure to thrive. Here, we present a series of 3 neonates with CPA managed at our center in the year 2020 (Jan 2020-December 2020). The associated skin blisters in all 3 cases likely represent Carmi syndrome. It is the name given to a rare genetic disorder characterized by junctional epidermolysis bullosa (JEB) and pyloric atresia (PA). While one succumbed before any intervention, 2 of them underwent surgery. Though isolated CPA has a good prognosis, Carmi syndrome has a poor outcome, as observed in our series. We are presenting 3 neonates with likely Carmi syndrome, emphasizing that genetic screening and counseling are necessary in these cases.

CASE SERIES

Case 1: A 3-day-old, premature (34 weeks of gestation) male neonate was admitted to the neonatal ICU with multiple blisters over the body. Pediatric surgical opinion was sought in view of feed intolerance and non-bilious vomiting. X-ray abdomen showed a classical single bubble shadow without any distal gas (Fig. 1A). A diagnosis of CPA with associated Epidermolysis bullosa was made. The blood picture was suggestive of leukocytosis (18000 cells/mm3) (with a neutrophilic predominance of 78%) and thrombocytopenia (Platelet counts-40000 cells/mm3). C-reactive protein was raised (22 mg/dl). Blood culture revealed Acinetobacter sp., sensitive to Colistin. The child succumbed to sepsis before any surgical intervention could be done.

Case 2: A 7-day-old, full-term gestation male baby presented with complaints of multiple blisters over the body and inability to feed. The initial history given by attendants pointed to a thermal injury by the warmer. X-ray abdomen was suggestive of classical pyloric atresia, and in association with skin blisters, a retrospective diagnosis of associated Epidermolysis bullosa was made. Exploratory laparotomy revealed Type 2 CPA (Fig. 1B) and retro-colic posterior gastrojejunostomy (GJ) was done, after excluding distal atresia. The neonate did not tolerate feeds in the post-operative period and had multiple episodes of bilious vomiting. The baby underwent re-exploration after waiting for 2 weeks and loop GJ was converted to Roux-en-Y GJ. Oral feeds were started on POD 3 and

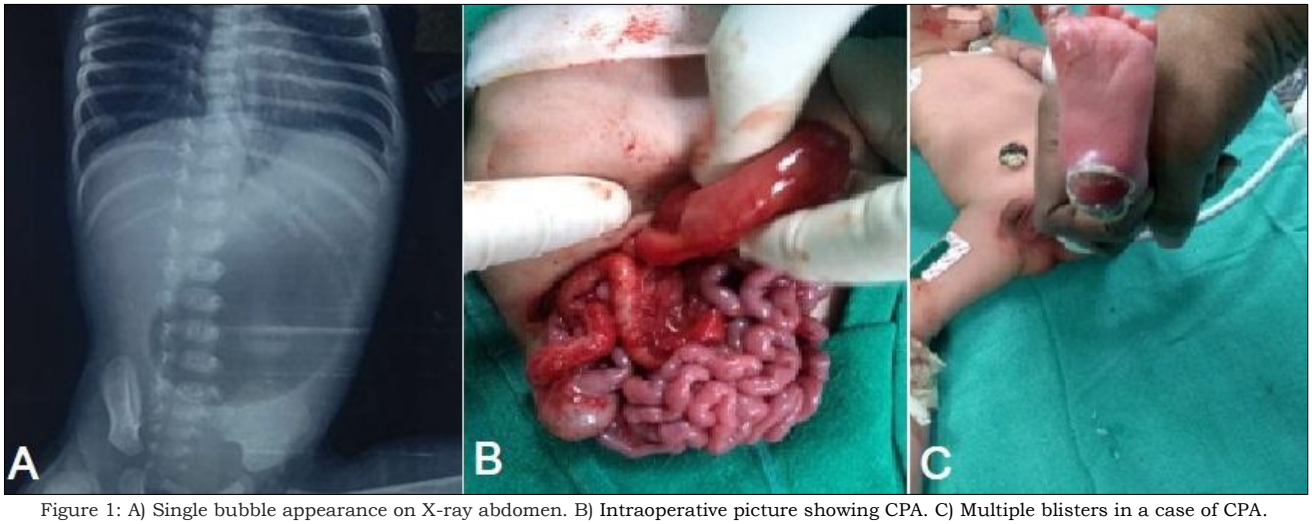

Figure 1: A) Single bubble appearance on X-ray abdomen. B) Intraoperative picture showing CPA. C) Multiple blisters in a case of CPA.

discharged by POD-7. The baby was lost to follow-up after 2 months of age. A later inquiry over the phone revealed that the baby had succumbed at the age of 3 months to an unknown cause.

Case 3: A preterm (33 weeks of gestation), low birth weight (1.2 kg) male baby was brought on day 2 of life with upper abdominal distension, skin blisters, and vomiting of milk (Fig. 1C). X-ray abdomen showed a single bubble appearance and a diagnosis of CPA with Epidermolysis bullosa was made. Laparotomy revealed type 1 CPA for which Heineke-Mikulicz pyloroplasty with diaphragm excision was done, after confirming distal patency of the bowel. Oral breastfeeds were started on POD-5. The discharge from the hospital was delayed due to the development of Acinetobacter sepsis, with blood picture showing raised CRP (42 mg/dl), and leukocytosis (TLC-19500 cells/mm3) with thrombocytopenia (Platelet counts- 45000 cells/mm3). 2D-Echo and ultrasound abdomen ruled out associated cardiac and renal anomalies table: 1.

Table 1: Tabular presentation of reported 3 cases of Carmi syndrome.

	Case 1	**Case 2**	**Case 3**
Day of presentation	Day 3	Day 7	Day 2
Mode of presentation	Feed intolerance and skin blisters	Feed intolerance and skin blisters	Abdominal distension, feed intolerance, and skin blisters
Surgery done	-	Retrocolic GJ, with conversion to Roux-en-Y GJ at re-exploration	Pyloroplasty
Post-op recovery	-	Delayed due to sepsis, reoperated on POD-15 and anastomosis revised to Roux-en-Y GJ	Oral feeds started on POD-5
Hospital stay	3 days, died due to sepsis	35 days	24 days
Skin care	Padding of pressure points, blister care, topical antibiotics	-do-	Skin blisters healed well.
Follow-up period	-	Lost to follow-up after 2 months. [Expired at 3 months of age]	1 year 6 months

In none of the 3 reported cases, could a skin biopsy be done, in view of the non-availability of genetic studies and immunofluorescence at our center. The diagnosis of Carmi syndrome was based on findings of congenital pyloric atresia with skin lesions. Genetic screening or immunofluorescence microscopy is recommended in these cases.

DISCUSSION

CPA is known to occur in 1 in 100000 live births. It constitutes about 1% of all gastrointestinal atresia. It equally affects male and female patients.[1] CPA has been associated with low birth weight and polyhydramnios, each reported in up to 60% of the patients.[2] Antenatal ultrasound may raise suspicion of CPA as early as 10 weeks, with polyhydramnios and dilated stomach shadow.

CPA was first reported in the year 1749 by Calder. It may present as an isolated anomaly or be associated with other systemic anomalies. There are 3 types of CPA. In type 1, there exists a pyloric membrane or diaphragm at the pylorus. The pyloric tissue is replaced by a solid cord of tissue in type 2 CPA. Type 3 CPA is characterized by a mesenteric gap between the stomach and duodenum. The type 1 CPA is the most common type of CPA (57%) while the type 3 CPA is the rarest (9%).

The etiology of CPA is largely unknown. Embryologically, it occurs due to developmental aberration at 5 to 12 weeks of gestation.[3] The most accepted theory of failure of canalization of a pyloric tube was given by Tandler.[4] Lowe and Bernard proposed a mechanical cause or vascular accident as an etiology, similar to jejunoileal atresia.[5] Weber [6] and Chang et al. [7,8] explained the association between CPA and Epidermolysis bullosa and proposed that this association results from an intrauterine mucosal injury at junctional EB, with subsequent ulceration and inflammatory response.

Other associated anomalies like ureteral and renal anomalies (duplicated pelvicalyceal system, hydronephrosis/hydroureteronephrosis, dysplastic or multicystic kidney, or/and absent bladder), milia, nail dystrophy, aplasia cutis congenita, esophageal atresia, and multiple colonic atresias have been reported in 40–55% of the cases.[9,10] There were no other associated anomalies in our 2 operated cases.

The treatment of CPA is governed by the type of atresia. Type 1 and 2 CPA are treated using the technique of Heineke–Mikulicz pyloroplasty (excision of membrane/tissue followed by transverse closure of longitudinally opened canal). For type 3 CPA, the treatment of choice is gastro-duodenostomy or gastro-jejunostomy. Per-operatively, the patency of the distal intestine needs to be confirmed to exclude associated distal intestinal atresia. Isolated CPA has a good prognosis. The mortality exceeds 50% when associated with severe and often fatal anomalies.[9]

Carmi Syndrome is the name given to an association of epidermolysis bullosa (EB) and congenital pyloric atresia (CPA).[11] EB is a group of hereditary skin disorders with characteristic vesicular lesions at or shortly after birth, targeted to areas of friction/minor trauma. It is categorized as EB simplex (EBS), junctional EB (JEB), and dystrophic EB (DEB). EB has sub-epidermal separation through the lamina lucida causing mechano-bullous lesions and is generally fatal. EB has genetic predilections and may run in families. The decision regarding the prognosis and future pregnancies should be discussed with the parents, along with genetic counseling. It is possible to diagnose EB by the electron microscopy of fetal-skin biopsy, carried out at 19 weeks gestation. [12] The parents of case 2 of our series had revealed over the phone that they recently had another sibling with similar features (Carmi Syndrome) but could not be operated on in view of travel restrictions due to the Covid pandemic and expired at home. The family was advised for genetic counseling. A tabular presentation of reported Carmi syndrome in Literature is shown in table 2.

Table 2: A tabular presentation of Carmi syndrome cases reported in the literature from 2010 till date

S. No.	Authors and Journal	Outcome
1.	Joshi M, Krishnan L, Kuruvila S. Large gastric perforation in Carmi syndrome: a morbid complication in a rare association. J Neonatal Surg. 2012; 1(4).	1 case operated. The outcome is not known as the patient went LAMA.
2.	Bıçakcı U, Tander B, Cakmak Çelik F, Arıtürk E, Rızalar R. Pyloric atresia associated with epidermolysis bullosa: report of two cases and review of the literature. Ulus Travma Acil Cerrahi Derg. 2012;18:271-3	2 operated cases of Carmi syndrome. Both died in the post-operative period due to sepsis.
3.	Son TN, Hoan VX. Laparoscopic management of pyloric atresia in a neonate with epidermolysis bullosa. J Laparoendosc Adv Surg Tech A. 2013;23:649-50	Successful laparoscopic management in 1 neonate
4.	Marjanovic Z, Slavkovic A, Djordjevic I. Syndromic Association of Pyloric Atresia and Epidermolysis Bullosa. West Indian Med J. 2013; 62(2):149.	1 case was successfully operated on but had late expiry due to respiratory distress syndrome
5.	Mithwani AA, Hashmi A, Adil S. Epidermolysis bullosa and congenital pyloric atresia. Case Reports. 2013 Sep 24; 2013:bcr2013201207.	1 operated case of Carmi syndrome, expired in the early postoperative period.
6.	Gupta R, Soni V, Mathur P, Goyal RB. Congenital pyloric atresia and associated anomalies: a case series. J Neonatal Surg. 2013; 2:40	2 cases had carmi syndrome, out of which one succumbed to sepsis
7.	Parelkar SV, Kapadnis SP, Sanghvi BV, Joshi PB, Mundada D, Shetty S, et al. Pyloric atresia-Three cases and review of the literature. Afr J Paediatr Surg. 2014; 11:362-5.	3 cases operated out of which 1 died of septicemia
8.	Farmakis SG, Herman TE, Siegel MJ. Congenital pyloric atresia, type B; with junctional epidermolysis bullosa. J Perinatol. 2014;34(7):572-3	1 case operated. Outcome not documented
9.	Al-Salem AH, Abdulla MR, Kothari MR, Naga MI. Congenital pyloric atresia, presentation, management, and outcome: a report of 20 cases. J Pediatr Surg. 2014; 49(7):1078-82.	Reported 8 cases of Carmi syndrome; 1 died pre-operatively and 7 underwent surgery. Out of 7, 6 succumbed to sepsis.
10.	Ko L, Griggs CL, Mylonas KS, Masiakos PT, Kroshinsky D. A nonlethal case of junctional epidermolysis bullosa and congenital pyloric atresia: compound heterozygosity in a patient with a novel integrin beta 4 gene mutation. J Pediatr. 2018; 193:261-4.	1 case was operated and the non-lethal outcome
11.	Márquez K, Rodríguez DA, Pérez LA, Duarte M, Zárate LA. Epidermolysis bullosa with pyloric atresia: Report of two cases in consecutive siblings. Biomedica. 2021;41:201-207	Carmi syndrome in 2 consecutive siblings, with fatal outcomes in both

The incidence of EB alone is 1/300,000. Healthy long-term survival is documented in the literature despite high mortality with this combination.[7] EB has no definitive treatment, usually managed with supportive care. It includes derma care of lesions, with appropriate dressing and infection control. Nutritional supplements and topical steroids may be used for local inflammation. One of the operated cases expired after loss to follow-up (most likely due to sepsis) and another is in follow-up for the last 1.5 years and gaining weight, without any recurrence of skin lesions.

A systematic literature review of Carmi syndrome by Mylonas KS et al included 100 patients out of 63 studies that showed an equal prevalence of type 1 and 2 CPA. Overall mortality was 74.5%, with 50% of deaths occurring in the neonatal period. Out of 73 patients who underwent surgery, 49 died (67.1%).[13] They suggested that detailed genetic mutation studies can be used to guide surgical intervention, as well as family planning. Hon KL et al reported late deaths in 3 cases of EB and found on a review of the literature that sepsis/septicemia is one of the common causes of death in these patients and stressed active skin care.[14].

CONCLUSION

Carmi syndrome should be kept as a differential diagnosis in neonates with skin blisters and feed intolerance. Early recognition and prompt medical and surgical management do contribute to a successful outcome. We propose that all neonates presenting with congenital pyloric atresia should be screened for multiple anomalies and undergo skin biopsy (at the time of surgery) with immunofluorescence microscopy to describe the type of associated EB for prognostication. Genetic screening should be offered to parents of babies with CPA with the syndromic association.

Acknowledgements: Nil

Conflict of Interest: One of the authors is editor of the journal. However, the manuscript is handled independently by another editor and the specific author is not involved in the decision making about the manuscript.

Source of Support: Nil

Consent to Publication: Author(s) declared taking informed written consent for the publication of clinical photographs/material (if any used), from the legal guardian of the patient with an understanding that every effort will be made to conceal the identity of the patient, however it cannot be guaranteed.

Author Contributions: Author(s) declared to fulfill authorship criteria as devised by ICMJE and approved the final version. Authorship declaration form, submitted by the author(s), is available with the editorial office.

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