IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Case Report

Prenatal Diagnosis of an Unusual Phenotype of Cantrell's Pentalogy: Case Report, and Literature Review

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ABSTRACT

Background: Cantrell's pentalogy (CP) is a rare congenital disease caused by morphological changes in the mesoderm. Defects of the lower sternum with ectopia cordis, midline supraumbilical abdominal wall, anterior diaphragm, diaphragmatic pericardium, and cardiac alterations are the related symptoms.

Case report: The case report is a newborn boy with a prenatal diagnosis of abdominal wall defect caused by pentalogy of Cantrell class 1 and initial measures were taken to prevent adverse outcomes. Congenital syndromic disease, such as CP, is likely to be treated with early prevention and adequate prenatal controls. Also, early diagnosis facilitates effective clinical and surgical management and thus leads to a positive prognosis.

Conclusion: Finally, it has been established that proper decision-making about therapeutic possibilities during the early years may improve the quality of life and longevity in this population.

Keywords: Congenital abnormalities, Ectopia cordis, Heart diseases, Hernia, Infant, Newborn, Pentalogy of cantrell, Umbilical

Introduction

In 1958, Cantrell et al. associated a set of five phenotypic traits in 21 cases, collectively referred to as the Cantrell's Pentalogy (CP) (OMIM: 313850). These five traits are defects in the congenital heart (E.g. Tetralogy of Fallot), the supraumbilical abdominal wall (E.g. omphalocele), the lower part of the sternum (E.g. Agenesis), the diaphragmatic pericardium (E.g. Ectopia Cordis) and the anterior diaphragm (Anterior diaphragmatic herniation) (1, 2,3 4). However, very few cases report the complete variant of this syndrome, which is related to the five above-mentioned phenotypic traits. The literature review indicates that this specific variant is repeated once every 65,000 to 200,000 live births (1, 5, 6). Its prognosis is closely related to early prenatal diagnosis and treatment (1, 2, 7–14).

In 1972, Toyama proposed additional classification of the syndrome: class I, confirmed diagnosis with all five present defects; class II, probable diagnosis with four noted defects (including intracardiac and ventral abdominal wall abnormalities); and class III, incomplete expression when various combinations of defects are present, always including a sternal anomaly (1, 2, 3, 6, 15–17). The theory of Cantrell continues to be accepted despite multifactorial errors that predominate during mesodermal differentiation during the weeks 14-18 of pregnancy (1, 2, 3, 18); Although, alterations in the wall closure may occur as early as the fourth week of pregnancy (4,15). Another theory relies on molecular defects of the X chromosome, in which parallel and phenotypic traits different from the previously mentioned have been reported in 28% of CP patients. The etiology of this syndrome raises

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Please cite this paper as:
Aivasovsky-Trotta I, Vergara-Cardenas S, Ferrer-Marcano A, Lorena Rincones-Rojas L, Carolina Prieto-Soler C, Ana Bracho-Fernández A, Isabel Fernández-González I, Gustavo Celis L. Prenatal Diagnosis of an Unusual Phenotype of Cantrell's Pentalogy: Case Report, and Literature Review. Iranian Journal of Neonatology. 2021 Oct: 12(4). DOI: 10.22038/IJN.2021.53668.1983

further doubts regarding the accepted theories of pathogenesis which may be a possible starting point for subsequent studies (4).

This article aims to expose the case of a newborn patient with a definitive diagnosis of Pentalogy of Cantrell class I to acquaint and analyze the current literature on early diagnosis strategies, and surgical treatment possibilities.

Methods

Ethical statements, Consent, and Permits

This study was conducted under the ethical principles of the Declaration of Helsinki to ensure the interests of the subjects. Necessary information was provided, doubts were clarified and participants signed informed consents before starting the research.

Methodology

Medical records of a male neonate were observed and a physical examination was performed with parental consent. Also, paraclinical studies including obstetric ultrasounds, abdominal wall ultrasound, echocardiogram, chest tomography, and karyotyping were evaluated to diagnose the anomaly. Subsequently, database research was conducted in Pubmed, Clinical Key, and OVID, using "MeSH", emphasizing recent literature with a 20-year limit, including older but relevant ones to the exposure and illustration of the disease.

Case report

The case study was a 13-day-old baby boy who was admitted for evaluation by genetic medicine. He was born to healthy, non-relative parents with no history of inherited diseases. The 25-year-old primigravida patient failed to have enough prenatal visits since the beginning of her pregnancy. During the third trimester of pregnancy, an obstetric ultrasound examination was performed due to abnormal uterine bleeding, vast abdominal wall defect, and abnormalities within the cardiac silhouette. Diagnosing thoracoabdominal wall defect (Onphalocele) may be due to Cantrell's Pentalogy. The patient was delivered at term through cesarean section, weighing 2.900 g and a height of 48 cm, and APGAR scores were 8 and 9 at first, and five min after birth, respectively. A prominent defect, completely covered by a matte membrane, was visible on the anterior abdominal wall (Figure 1). Therefore, he was admitted to the perinatal special care unit for cardiac evaluation, pediatric surgery, genetic counseling, oxygen, and prophylactic antibiotic therapies.

An echocardiogram was performed to define the anatomical characteristics of congenital heart disease, determine cardiomegaly for other anomalies such as Dextroposition, a 4.1 mm interatrial communication / persistent foramen ovale, and a 4.4 mm interventricular communication in all of the above with transposition of the great vessels without compromising the pulmonary trunk rather than the efferent branches of the aorta. Chest and abdomen tomography with IV contrast identified the extensive thoracoabdominal defect which included the midline of the anteroinferior wall of the chest and the anterosuperior wall of the abdomen, as well as the absence of the distal third of the sternum body and the xiphoid appendix. The absence of the diaphragmatic pericardium and anterior diaphragmatic defect was observed through this 86.6 mm defect in the upper abdomen. Other vascular malformations included

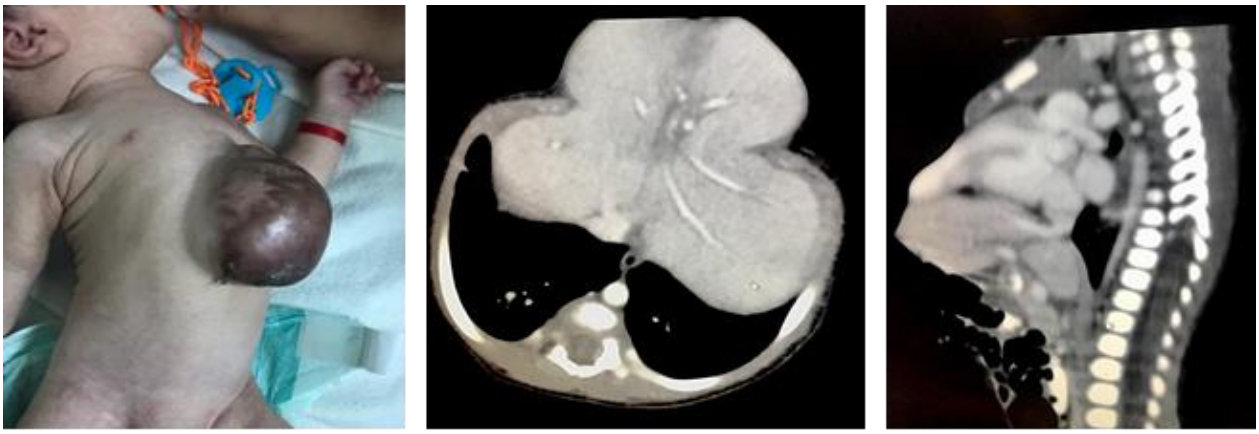

Figure 1. *Phenotype VS. Contrast CT scan (Transverse Cut and Sagittal).* A prominentn thoraco-abdominal defect covered by a pigmented and opaque membrane. In contrast, CT images findings, as a significant finding, sternal agenesis with cardiac apex protrusion through the defect.

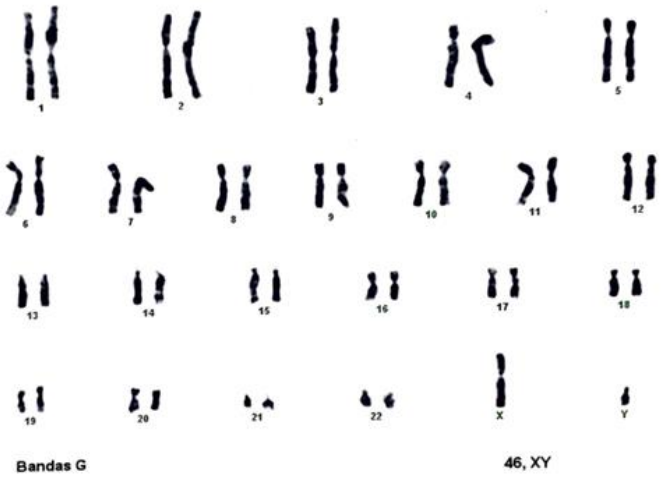

Figure 2. G-banding karyotyping

a common origin of carotid arteries and subclavii with aberrant right subclavian artery which is located behind the trachea and esophagus (Figure 1). Finally, G-banding karyotyping was performed with 20 metaphases and 46XY without any other anomalies (Figure 2).

A definitive diagnose of Cantrell's Pentalogy type I was prenatally established and confirmed by CT scan and echocardiography based on the extensively characterized phenotype. Acute heart failure, clinical signs of water overload, and low expenditure should be monitored during hospitalization. In the meantime, it was decided to set up ambulatory monitoring of the patient's condition with a multidisciplinary approach of cardiology, cardiovascular surgery, pediatric surgery, and perinatology. The patient was further discharged without any other complications.

Discussion

This particular case presented for reviewing the literature to establish, collect and update the knowledge of this infrequent disease. The quality of life of patients with CP and their caregivers was ensured by defining appropriate management and available treatment.

As stated, James R. Cantrell, Haller, and Ravitch, in 1958 defined this syndrome by describing and analyzing 16 cases. They concluded that it was *"A congenital malformation syndrome involving the abdominal wall, sternum, diaphragm, pericardium, and heart"* (1). They also compared five of their cases with previous ones to develop their first theory of the embryological origin. Moreover, they eventually proposed a new treatment for early and drastic surgical correction of the exposed structures, including thoracic, abdominal, and diaphragmatic defects; although, this may be debated and even overruled by some of the available scientific evidence. (1, 2, 3)

Epidemiology

The severity of CP may vary from person to person, and not gender-related, though it is believed that more severe symptoms may develop in female cases (14). The exact prevalence is unknown; however, the figures report an approximate frequency of an affected individual per 65,000-200,000 live births (19, 20). It is an orphan disease worldwide and Colombia with only three cases since 2016 is also no exception (21, 22).

Classification of the phenotypical presentations of CP by Toyama is still being widely used, and most cases reported worldwide range between classes 2 or 3 with very few cases of class 3, such as the present case (1, 4, 14, 16).

In most cases, multifactorial and unclear etiologies may cause this syndrome. However, an X-linked dominant inheritance with some cases of trisomy 13, 18, and teratogenic exposure has been repeatedly reported s the possible causative agent (4, 20, 23). Moreover, some studies have determined the role of mutations in the PORCN gene (locus Xp11.23) that may alter the acylation of ligands in the Wnt signaling pathway, leading to the inadequate formation of the ventral abdominal wall in patients with Goltz-Gorlin syndrome (4, 18, 23) and a single case with ALDH1A2 gene mutation. Additionally, mechanical teratogenesis has been described in one case of twin pregnancy (23) as well as the formation of fibrous amniotic bands that alter adequate embryological development (12).

Embryology

The embryological origin of the wide spectrum of changes in the normal thoracoabdominal structures is tightly related to errors in the early embryonic development of the mesoderm that occur between 14 to 18 days of pregnancy (1, 6, 16, 23). Cantrell suspected that the cause of the resulting defects was a major defect in the development of the transverse septum and the immediately adjacent somatic and splanchnic mesoderm which are responsible for the formation of the anterior diaphragm, lower pericardium, and cardiac structures. Another hypothesis suggests a failure in normal migration of the primordial sternum which leads to inadequate fixation of the anterior abdominal musculature in this structure and abdominal wall defects which is related to the abnormal closure of the ventral and lateral abdominal wall in the fourth week of embryonic development (1, 4, 15).

Clinical Characteristics

Pentalogy of Cantrell is an uncommon congenital abnormality characterized by a wide range of morphological defects of the thoracoabdominal wall, the lower part of the sternum, diaphragm, diaphragmatic pericardium, and cardiovascular disorders (1, 2, 4, 6).

Among the specific manifestations of this disease are anterior diaphragmatic defects, such as diaphragmatic hernias with or without abdominal herniation, which may be related to the absence of the apical pericardium in some cases. Furthermore, alterations in the lower part of the sternum have been documented with a complete or partial absence of the xiphoid process (20).

This spectrum of defects which is classified into four types according to their location and prevalence is the direct culprit of the protrusion of the heart (Ectopia Cordis) through the chest wall. Isolated chest and abdominal protrusion of the heart are seen in 60% and 30% of all the cases, respectively. In addition, Thoracoabdominal protrusion is seen in 7% of cases and has been associated with better surgical and clinical prognosis. Finally, an isolated cervical protrusion is seen in only 3% of all cases which is not compatible with life (14, 24). Intracardiac malformations include a wide spectrum such as ventricular or atrial communications, tetralogy of Fallot, left ventricle hypoplasia syndrome, ductus arteriosus, and diverticulum. Another key finding, as seen in our patient, is the alteration of the supraumbilical abdominal wall causes the protrusion of abdominal organs (Omphalocele) (1, 2, 3, 4, 20, 24 – 26) (figure 1). Furthermore, someunrelated neurological findings such as Anencephaly, Encephalocele, Dysgenesis of the Corpus Callosum, Craniorachischisis, as well as other alterations such as Renal dysplasia, Renal agenesis, Syndactyly, Micrognathia, Gastroschisis, Intestinal Malrotation, biliary atresia has also been reported (7, 25).

As evidenced in our patient, the main hallmark is an omphalocele associated with Ectopia Cordis, which shapes this syndromic entity with the abdominal and thoracic wall defect as well as the cardiovascular malformations (Table 2)

Diagnostic Approach

Prenatal diagnosis is crucial for establishing a timely response to possible negative outcomes of this syndrome, as well as determining the prognosis and making perinatal decisions that

Table 1. Cantrell's pentalogy; spectrum of signs and symptoms and their incidence (25)

Defects seen in Cantrell's Pentalogy	Findings
Diaphragmatic pericardium	Complete pericardial agenesis Partial pericardial agenesis
Inferior diaphragmatic anomalies	Congenital diaphragmatic hernia
Congenital heart defects	Interventricular Communication (72-100%) Interatrial communication (34,6-53%) Pulmonary stenosis or atresia (31,5-33%) Ventricular diverticulum (17-50%) Tetralogy of Fallot (17-20%) Dextrocardia (15%) Great Vessels Transposition (86,3%)
Supraumbilical abdominal wall defects	Omphalocele (74,5%) Ectopia Cordis
Lower-sternum abnormalities	Agenesis or separation of the sternum Partial separation of the lower sternum

Table 2. Phenotypical findings of the patient. Type 1 Cantrell's Pentalogy

Cantrell·s Pentalogy	Findings in the patient
Supra-umbilical abdominal wall defects	Omphalocele
Congenital heart defects	Interatrial communication (4.1 mm) Interventricular communication (4.4 mm)
Inferior diaphragmatic anomalies	Congenital diaphragmatic hernia
Lower-sternum defects	Ectopia Cordis, Agenesis of the sternum including the xiphoid process
Diaphragmatic pericardium	Complete pericardium agenesis

could benefit the patient and family. In general, the diagnosis is initially established during prenatal care check-ups, especially in the first trimester, while performing 2D and Doppler Ultrasound examinations, which is the first-choice method of assessing morphological defects such as Ectopia Cordis and Abdominal wall defects. Once an initial approach has been established, other confirmatory tests such as 3D ultrasound and MRI are used to diagnose and characterize more complex malformations that may not be seen with conventional ultrasound devices (20, 27, 28). Although these two defects probably suggest a possible and definitive diagnosis of CP, physicians should consider the Isolated Ectopia Cordis and Amniotic band syndrome as the main differential diagnosis. Other radiological studies such as the multi-shortening scanner and nuclear magnetic resonance imaging can be used for PC studies (11, 29 – 31).

Once the patient is delivered, further examinations should be performed to determine his condition, ascertain a definitive postnatal diagnosis, and prepare a possible surgical approach. Chest x-ray, transthoracic echocardiography (TTe), CT scan, angiography, and MRI may be performed for this matter (16, 27). TTe and post-natal angiography are crucially important to determine possible surgical options and the prognosis of the newborn (27).

Treatment

The major goals for the surgical treatment of this disease are the correction of intracardiac defects, ventral hernia, and diaphragmatic injuries. Although surgical ethics and intervention criteria that configure the possible abnormalities of this orphan syndrome have been very well established, there is no international consensus on the initial surgical approach in these patients. The order of surgical repair between the chest-abdominal defect and cardiac damage depends on clinical manifestations seen on the patient (27).

Intervention at a young age is more recommended than expectant and surgical management during adulthood (10). Nevertheless, it is also advised to wait at least 2 years for the growth of the chest cavity that decreases the risk of high intrathoracic pressure which may lead to unsatisfactory cardiac positioning (16). Of course, if there is cardiovascular involvement or hemodynamic instability, the early surgical approach would be questioned as the final decision is usually made depending on the patient's condition and the tests performed by the physician. (32)

Harring et al. reported a follow-up case of an 11-year-old patient with a complete phenotype who underwent the corrective surgical procedure of the chest wall with subsequent correction of the double outlet right ventricle. However, they did not internalize the heart due to the high risk of compressing such structures (9).

The final decision for our patient was conducting a close follow-up without an immediate surgical intervention as his family failed to have the support of the healthcare system for sustaining advanced procedures. Also, the patient required no immediate procedure to ensure his safety.

Prognosis

According to the literature, the prognosis of Cantrell's Pentalogy is generally poor and heavily relies on the severity of heart disorders. Surgical repair is mainly performed in infancy or childhood (20, 30). Causes associated with surgery such as tachyarrhythmia, bradycardia, hypotension, ruptured diverticulum, and heart failure are 50% of the most common causes of death (33). No recurrence of this syndrome has been reported in subsequent pregnancies (11).

Conclusion

Cantrell's Pentalogy directly determines neonatal health and well-being like many other congenital pathologies. An appropriate method of pregnancy was performed for the present case through prenatal control strategies aimed at eliminating this spectrum of malformations. The

diagnosis approach was established due to the clinical and socioeconomic conditions of the patients as a timely and premeditated perinatal plan based on the available evidence.

Despite the absence of standardized management criteria, a multidisciplinary and individualized approach to any case of Cantrell's Pentalogy is crucial due to the characteristics of the patient to improve the outcomes during early ages .

Acknowledgments

None.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of the present study.

References

1. Williams AP, Marayati R, Beierle EA. Pentalogy of Cantrell. Semin Pediatr Surg. 2019; 28(2):106-10.
2. Albu C, Staicu A, Popa-Stănilă RT, Milaş AC, Chiriac LB, Kovács TE, et al. Multidisciplinary approach of assessing malformed fetuses exemplified in a rare case of pentalogy of Cantrell associated with craniorachischisis, pulmonary extrophy and right-sided aortic arch with aberrant brachiocephalic artery. Rom J Morphol Embryol. 2018; 59(3):911-5.
3. Grigore M, Furnica C, Esanu I, Gafitanu D. Pentalogy of Cantrell associated with unilateral anophthalmia case report and literature review. Medicine. 2018; 97(31):e11511.
4. Smigiel R, Jakubiak A, Lombardi MP, Jaworski W, Slezak R, Patkowski D, et al. Co-occurrence of severe Goltz-Gorlin syndrome and pentalogy of Cantrell - Case report and review of the literature. Am J Med Genet Part A. 2011; 155(5):1102-5.
5. Chandran S, Ari D. Pentalogy of Cantrell: an extremely rare congenital anomaly. J Clin Neonatol. 2013; 2(2):95-7.
6. Kanasugi T, Kikuchi A, Uesugi N, Fukagawa D, Chida H, Sasaki Y, et al. Pentalogy of Cantrell in a monozygotic twin with a giant omphalocele firmly attached to the amniotic membrane: Successful prenatal diagnosis and cesarean delivery. Congenit Anom (Kyoto). 2018; 58(2):73-4.
7. Hubbard R, Hayes S, Gillis H, Lindsey S, Malhotra P, Wani T, et al. Management challenges in an infant with pentalogy of Cantrell, giant anterior encephalocele, and craniofacial anomalies: a case report. A A Pract. 2018; 11(9):238-40.
8. Kim CW, Cho HM, Son BS, Kim DH. Neo-sternum reconstruction using costal cartilage approximation and small Permacol patch repair in the treatment of Cantrell pentalogy: a case report. J Cardiothorac Surg. 2015; 10(1):40.
9. Harring G, Weil J, Thiel C, Schmelzle R, Mueller GC. Management of Pentalogy of Cantrell with complete ectopia cordis and Double Outlet Right Ventricle. Congenit Anom (Kyoto). 2015; 55(2):121-3.
10. Mizelle KM, Holtzlander M, Ajaz F, Mcconnell PI, Splaingard ML. Adult survivor with repaired complete pentalogy of Cantrell. World J Pediatr Congenit Hear Surg. 2014; 5(4):586-8.
11. Cortés H, Vélez JF. Prenatal ultrasonographic diagnosis of Cantrell's Pentalogy. Colombian J Obstet Gynecol. 2003; 54(1):13-6.
12. Saldarriaga-Gil W, Ayala-Zapata S, Ramírez-Cheyne JA, Isaza C. Pentalogy of Cantrell and amniotic bands: a case report and review of the literature. Rev Colombiana Obstet Ginecol. 2014; 65(3):243-9.
13. Grigore M, Micu R, Matasariu R, Duma O, Chicea AL, Chicea R. Cantrell syndrome in the first trimester of pregnancy: imagistic findings and literature review. Med Ultrason. 2020; 22(2):189-6.
14. Swarray-Deen A, Seffah JD, Antwi-Agyei DA. Two cases of pentalogy of Cantrell diagnosed antenatally at Korle Bu Teaching Hospital, Accra. Ghana Med J. 2017; 51(4):191-5.
15. Kunapinun N, Treetipsatit J. Discordant anomalies with combined features of pentalogy of Cantrell and OEIS complex: a case report in Monochorionic Twins. Fetal Pediatr Pathol. 2017; 36(5):357-63.
16. Pirasteh A, Carcano C, Kirsch J, Mohammed TL. Pentalogy of Cantrell with Ectopia Cordis: CT findings. J Radiol Case Rep. 2014; 8(12):29-34.
17. Naburi H, Assenga E, Patel S, Massawe A, Manji K. Class II pentalogy of Cantrell. BMC Res Notes. 2015; 8(1):318.
18. Snowball J, Ambalavanan M, Cornett B, Lang R, Whitsett J, Sinner D. Mesenchymal Wnt signaling promotes formation of sternum and thoracic body wall. Dev Biol. 2015; 401(2):264-75.
19. Mallula KK, Sosnowski C, Awad S. Spectrum of Cantrell's pentalogy: case series from a single tertiary care center and review of the literature. Pediatr Cardiol. 2013; 34(7):1703-10.
20. Saldarriaga W. Pentalogy of cantrell: case report. Rev Salud Uninorte. 2014; 30(3):505-12.
21. Orphan-rare diseases event report, Epidemiological Period III. National Institute of Health. Available at: URL: https://www.ins.gov.co/buscador/Informesdeevento/ENFERMEDADES%20HUÉRFANAS-RARAS%20PE%20III%202019.pdf#search=cantrell; 2019.
22. Prevention of noncommunicable diseases Orphan diseases. Minsalud Colombia. Available at: URL: https://www.minsalud.gov.co/salud/publica/PENT/Paginas/enfermedades-huerfanas.aspx); 2019.
23. Salinas-Torres VM, De La O-Espinoza EA, Salinas-Torres RA. Severe intrauterine amputations in one dichorionic twin with pentalogy of Cantrell: Further evidence and consideration for mechanical teratogenesis. Pediatr Dev Pathol. 2017; 20(5):440-3.
24. Madžarac V, Matijević R, Škrtić A, Duić Ž, Fistonić N, Partl JZ. Pentalogy of Cantrell with unilateral kidney evisceration: a case report and review of literature. Fetal Pediatr Pathol. 2016; 35(1):43-9.
25. Jnah AJ, Newberry DM, England A. Pentalogy of

Cantrell: case report with review of the literature. Adv Neonatal Care. 2015; 15(4):261-8.
26. Martins CF, Serras I, Santos AV, Braga AC. Pentalogy of Cantrell: the complete spectrum. BMJ Case Rep. 2014; 2014:bcr2014207556.
27. Elí C, Rodríguez AM, Rodríguez IM, Moreno F, Colina A, Omm C. Pentalogy of Cantrell, incomplete diagnosis. casO report. Rev Facul Med Univ Andes. 2009; 18(2007):114-8.
28. Rodriguez E, Brenes G. Pentalogy of incomplete cantrell. Rev Centroam Obstet Gynecol. 2015; 20(4):103-5.
29. Singh N, Bera ML, Sachdev MS, Aggarwal N, Joshi R, Kohli V. Pentalogy of Cantrell with left ventricular diverticulum: a case report and review of literature. Congenit Heart Dis. 2010; 5(5):454-7.
30. Pachajoa H. Cantrell's pentalogy in the first twin from a monozygotic twin pregnancy: a case presentation and literature review. Rev Colombiana Obstet Ginecol. 2011; 62(1):94-7.
31. Kaul B, Sheikh F, Zamora IJ, Mehollin-Ray AR, Cassady CI, Ayres NA, et al. 5, 4, 3, 2, 1: embryologic variants of pentalogy of Cantrell. J Surg Res. 2015; 199(1):141-8.
32. Zhang X, Xing Q, Sun J, Hou X, Kuang M, Zhang G. Surgical treatment and outcomes of pentalogy of Cantrell in eight patients. J Pediatr Surg. 2014; 49(8):1335-40.
33. Yang Y, Jiang Z, Ding F. One-stage surgical treatment for Cantrell syndrome without repairing the left ventricular diverticulum: a case report. Cardiol Young. 2014; 26(1):191-3.