Case Report

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Duplication Cysts and Autoimmune Hemolytic Anemia: An Association or a Coincidence?

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ABSTRACT

Duplication cysts are rare congenital anomalies of the gastrointestinal tract and the occurrence of multiple such cysts is an extremely rare occurrence. Autoimmune hemolytic anemia is an extremely unusual manifestation of these duplication cysts. Herein, we report a case with two duplication cysts (one cyst in the thorax; another in the abdomen) complicated with autoimmune hemolytic anemia. This patient was a five year-old-male child who presented with congestive cardiac failure due to severe anemia (which, on evaluation, was diagnosed as autoimmune hemolytic anemia). Imaging studies (chest radiograph and computed tomography) revealed duplication cysts in the chest and abdomen. Anemia flare-up was noted in the patient despite two months of prednisolone therapy (2 mg/kg/day) and two high dose intravenous methylprednisolone pulse therapy courses (30 mg/kg/day for 5 days each). The steroid refractory autoimmune hemolytic anemia responded to rituximab (375 mg/m2 body surface area/week for 4 weeks). Four months after tapering off the steroid therapy, the patient did not experience flare-up of the anemia. To the best of our knowledge, this is the youngest and first pediatric age group patient to be reported, with a possible association between gastrointestinal duplication cysts with autoimmune hemolytic anemia.

Keywords: Autoimmune hemolytic anemia; Blood transfusion; Child; Computed tomography (CT); Duplication cyst; Paraneoplastic syndrome; Rituximab.

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INTRODUCTION

Gastrointestinal duplication cysts are rare congenital anomalies, which may be found anywhere along the gastrointestinal tract from the mouth to the rectum; most commonly seen in the ileum (33%).[1] They are usually detected prenatally on antenatal ultrasonography scan or in the first few years of life, but rarely in adulthood. Their location, size, mucosal pattern

and presence of complications produce varied clinical presentations.[2] Autoimmune hemolytic anemia (AIHA) occurring as a paraneoplastic phenomenon, is an extremely unusual consequence of these congenital cysts.[1,3] Herein, we report a case of gastrointestinal duplication cysts with steroid refractory AIHA. To the best of our knowledge, this is the youngest and first pediatric age group patient to be reported, with a possible association between gastrointestinal duplication cysts and AIHA.

CASE DETAILS/ REPORT

A five year-old-male child presented with the complaints of yellowish discolouration of eyes, passage of dark brown colored urine and progressively increasing pallor for the past 2 months. There was history of easy fatigability and exertional breathlessness, which had gradually progressed to breathlessness at rest. There was absence of history of any other medical or surgical ailments in the past. Before presenting to our institution, the child was transfused with packed red cell volume for four times (15 ml/ kg per transfusion) over a period of 10 days, in a nearby health care facility. During the process of evaluation, the chest radiograph done showed a round well defined radiopaque structure in the mediastinum extending towards left hemithorax, without any internal calcifications or air fluid levels. The child was referred to our institution for further investigations and management.

On admission to our institution, the child was afebrile, had tachycardia (135 beats per minute), tachypnea (35 breaths per minute), blood pressure of 98/50 mm Hg in the right arm in the supine position, and raised jugular venous pressure (7 cm). His weight was 9.5 kg (below -3 SD) and height was 100 cm (between -2 and -3 SD). He had severe conjunctival pallor and scleral icterus. The cardiovascular system examination revealed a soft systolic (hemic) murmur. Abdominal examination revealed firm and tender hepatomegaly of 4 cm (span of 9 cm) and firm splenomegaly (of 3 cm). The respiratory system examination revealed tachypnea with bilateral basal crepitations.

The preliminary investigations on admission revealed hemoglobin (Hb) of 3.9 g/dL with a corrected reticulocyte count of 16% (reference normal: 0.5-1.5%) and the peripheral smear showed fragmented red blood cells (RBCs), nucleated RBCs, macrocytes, poikilocytosis, polychromasia and dyserythropoesis. There was indirect hyperbilirubinemia (4.29 mg/dL) and serum lactate dehydrogenase was high (2678 U/L). The father was found to be a sickle trait on (the parent's) Hb electrophoresis study. These preliminary investigations are tabulated in Table 1.

Table 1: Investigations in the patient on admission to our institution. (*Indicates abnormal values)

Investigation	Results	Age appropriate reference range
HB	*3.2 g/dL	(11.5 – 14.5 g/dL)
Corrected reticulocyte count	*16%	0.5 - 1.5 %
Leukocyte count	18.1 X 10^3 cells/mm^3	4.0 - 12.0 X 10^3 cells/mm^3
Platelet count	300 X 10^3/mm^3	120 - 500 X 10^3/mm^3
Peripheral smear	Fragmented red blood cells (RBCs), nucleated RBCs, macrocytes, poikilocytosis, polychromasia, & dyserythropoesis	–
Serum electrolytes (Na+/K+)	133 / 3.7 mmol/L	134 – 143 / 3.3 – 4.6 mmol/L
BUN / serum creatinine	14.5 / 0.5 mg/dL	5 – 18 / 0.22 – 0.59 mg/dL
Serum total protein / albumin	7 / 4 g/dL	6.1 – 7.9 / 3.5 – 5.6 g/dL
Total / direct bilirubin / indirect bilirubin	*4.8 / 0.51 / 4.29 mg/dL	0 – 2.0 / 0 – 0.2 / 0.2 - 1 mg/dL
AST / ALT	8 / 7 U/L	15 – 50 / 5 – 45 U/L
Serum LDH	*2678 U/L	150 – 500 U/L
HIV ELISA test	Non-reactive	–
HBsAg/HCV	Negative	–
Parents Hb electrophoresis	Father: Sickle cell trait, Mother Normal	–

In view of severe anemia and congestive cardiac failure, he received 10 ml/kg of packed red cell transfusion with due precautions (post- transfusion Hb was 4.0 g/dL). One more packed red cell

transfusion was given at 15 ml/kg in the next 12 hours (post-transfusion Hb was 6.8 g/dL). With these transfusions, the congestive cardiac failure (CCF) showed improvement. Chest radiographs (frontal view Fig. 1 and lateral views) revealed a round well defined radio-opaque structure seen in the posterior mediastinum extending towards left hemithorax, without silhouetting cardiac border (on lateral view), without any internal calcifications or air fluid levels. Subsequently, the child underwent contrast enhanced computed tomography of the chest, which revealed a well defined homogenously hypodense cystic lesion in the left paravertebral region (Fig. 2) at the level T4 - T9, crossing the midline posterior to thoracic aorta and esophagus and seen in the prevertebral region at T8 - T10 level with minimal bulging towards the right hemithorax. It also caused compression of left lower lobe bronchus with a resultant subsegmental collapse of an anteromedial segment of the left lower lobe. Incidentally, a cystic lesion of similar morphology was also seen in the abdomen, arising from the small bowel mesentery at L1 - L4 level along the lesser sac, anterior to left kidney and extending to the lateral paracolic region (Fig. 3). No calcifications were noted in either of the cysts. The radiologist reported them as duplication cysts. However, within next two days, the child again developed signs of congestive cardiac failure with the repeat Hb of 4.9 g/dL, and hence the child was administered two packed red cell transfusions with a gap of 18 hours in between (15 cc/kg/transfusion). The direct and indirect Coomb's test revealed 4+ and 2+ titres respectively; however, direct antiglobulin test for warm and cold antibodies was negative. The child also tested negative for HIV antibodies, autoimmune lymphoproliferative syndrome workup, hepatitis serology and autoimmune antibodies (anti-nuclear antibodies and anti-double stranded DNA antibodies).

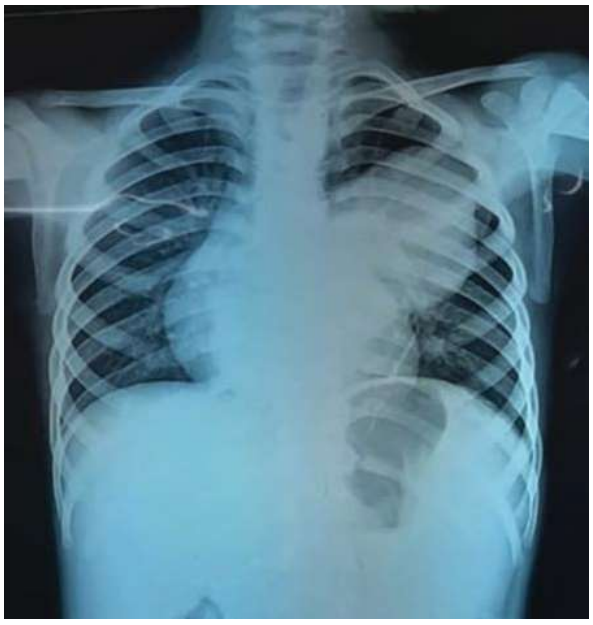

Fig. 1: Frontal radiograph of chest showing left-sided rounded well-circumscribed radio-opaque mass without any internal calcifications or air fluid levels.

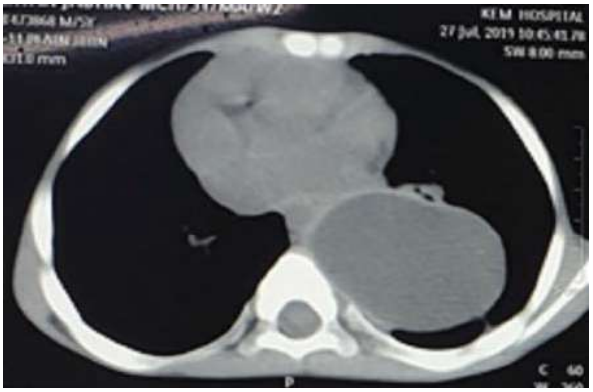

Fig. 2: Computed tomography of the chest showing a well defined homogenously hypodense cystic lesion in the left paravertebral region.

The patient was treated with high dose methylprednisolone, 30 mg/kg/day for 5 days (starting from 15th day of the hospital stay) and continued on oral prednisolone (2 mg/kg/day). The patient experienced flare-up of episodes of anemia and required repeated red cell transfusions, though there was a slight decrease in the frequency of the transfusions (Fig. 4). The patient received a repeat high dose methylprednisolone pulse therapy, 30 mg/kg/day for 5 days (on 38th day of hospital stay, 23 days after first methylprednisolone pulse therapy) and was continued on oral prednisolone (2 mg/kg/day). However, within the next 13 days (after second methylprednisolone pulse therapy), the child again started experiencing anemia flare-ups. In view of this steroid resistance, he was initiated on treatment with intravenous rituximab,

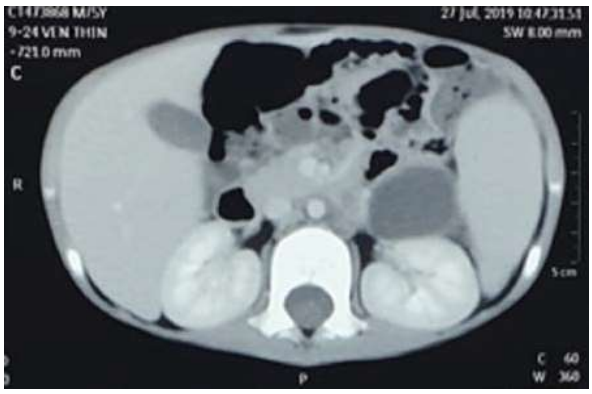

Fig. 3: Computed tomography of the abdomen showing a cystic lesion anterior to the left kidney.

375 mg/m2 body surface area/week (on 58th day of hospital stay) and the oral prednisolone (2 mg/kg/day) was continued. A bone marrow examination done before starting the rituximab revealed erythroid hyperplasia. The child showed gradual improvement in the hemoglobin and did not require repeat blood transfusions over the next 15 days of hospital stay (Fig. 4). A repeat direct and indirect Coomb's test showed a weakly positive test and negative test respectively. With this improvement, the child was discharged from the hospital (on 74th day of hospital stay, having completed 2 doses of intravenous rituximab) with a plan to give rituximab for a total of 4 weeks and to continue oral prednisolone (1.5 mg/kg/day) and to regularly follow-up. Over the next 2 months of follow-up, the child completed the intravenous rituximab therapy, tested negative for Coombs test and his oral steroids were gradually tapered off. On monthly follow-up over the next 4 months after stopping the steroid therapy, the patient did not experience any flare-up of anemia or brown colored urine, and he was going to school regularly and thriving well. In the interim period, the he had also developed hypertension secondary to long term steroid use, for which he was treated with oral nifedipine (0.3 mg/kg/day in two divided doses), which was eventually tapered off one month after stopping the steroid therapy.

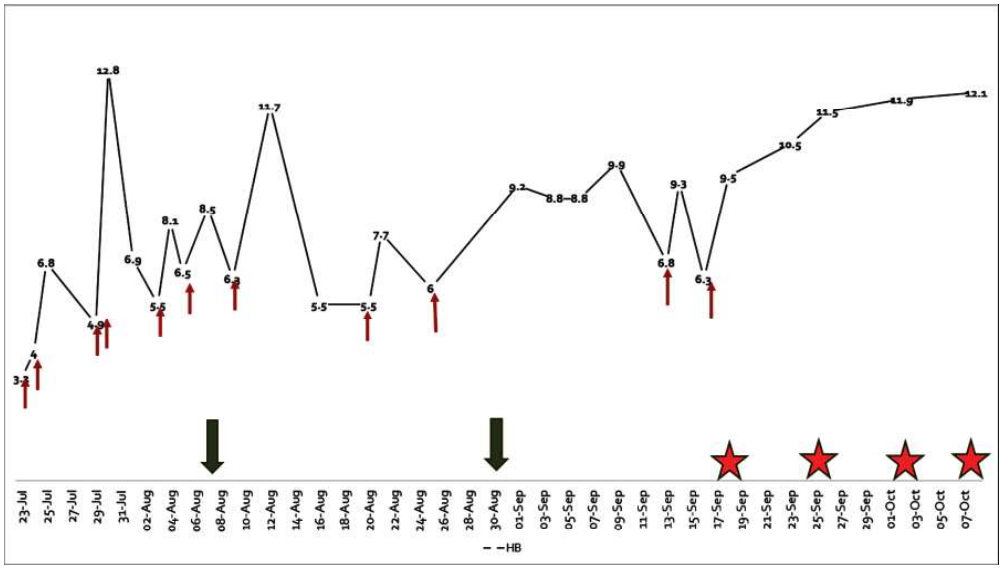

Fig. 4: Graph showing the trend of haemoglobin (Hb), thin red arrows directed upwards indicate blood transfusions given, thick green arrows directed downwards indicate the intravenous methylprednisolone pulse doses administered, and the red stars indicate the intravenous rituximab therapy.

DISCUSSION

Gastrointestinal duplication cysts are a rare congenital gastrointestinal malformation in children and adults.[1,2,3] They consist of foregut duplication cysts, small bowel (midgut) duplication cysts, and large bowel (hindgut) duplication cysts.[4] The occurrence of multiple such duplication cysts is a very rare occurrence (1–7%).[2] A patient can have multiple cysts within one segment of the gastrointestinal tract or rarely in two or more segments.[2] Duplication cysts most commonly occur in the ileum.[1,2] They may be contained within the gastrointestinal tract wall or may be extrinsic to it.[2,4]

Enterogenous cysts constitute 50-70% of foregut duplication cysts, while 7-15% of them are bronchogenic.[4] Foregut duplication cysts constitute 6-15% of primary mediastinal masses.[4] Esophageal duplication cysts are the second most common duplication cysts following the small bowel (ileum) duplications cysts, accounting for approximately 10-20% of the gastrointestinal duplication cysts.[2,4] As many as 80% of these lesions are diagnosed in childhood with the majority being symptomatic.[4,5] Most of the esophageal duplication cysts are located in the posterior inferior mediastinum.[4] In our patient, we could not characterise the mediastinal (foregut duplication) cyst, as a tissue biopsy could not be done due to the location of the cyst (as there was a possible risk of injury to vital organs during the biopsy procedure). Endoscopic ultrasound guided fine needle aspiration can be

employed to confirm the tissue diagnosis of these cysts, but there is a risk of infection of duplication cysts, bleeding and mediastinitis.[4] Incidentally, our patient was also found to have a second duplication cyst in the abdomen (lesser sac), which was neither symptomatic nor palpable clinically but picked up by computed tomography. We could not characterise this lesion as well, since the tissue biopsy could not be done.

These duplication cysts present with varied clinical manifestations depending upon their size, location, mucosal pattern and presence of complications (like bleeding, infection or ulcerations).[2,6] Autoimmune hemolytic anemia (AIHA) is a very infrequently reported complication in these cases. The exact reason behind the AIHA is not known but hypothesized to be a paraneoplastic manifestation.[1,3] There are only two reported cases of this rare association of duplication cyst and AIHA. Sreedhar et al. (2018) reported a 59 years old male with hepatitis C with enteric duplication cyst, who presented with steroid refractory warm AIHA. In this case, they could not give rituximab and other immunosuppressants because of active untreated hepatitis C with heavy viral load and chronic liver disease. An endoscopic biopsy was done after 2 years of follow-up, which revealed adenocarcinoma, and complete resection of the mass led to resolution of AIHA within 2 months.[3] Bennani et al. (2018) reported a 28-year-old male with gastric duplication cyst and steroid refractory autoimmune hemolytic anemia. The patient underwent a complete cyst resection and splenectomy during an exploratory laparotomy. The histological examination confirmed gastric duplication cyst without any signs of malignancy. Ten months after resection, the patient underwent complete remission and also tested negative for direct coomb's test.[1] Furthermore, because the splenectomy was performed at the same time and the hemolytic anemia resolution was obtained after the surgery, the authors could not give a definite conclusion on whether the excision of cyst or the splenectomy led to resolution of AIHA. In our patient, the pediatric surgeons declined to operate during the hospital stay as the child failed to maintain stable hemoglobin with steroids. After therapy with rituximab, the patient went into complete remission (evidenced by negative Coomb's test) and hence the surgery was deferred thereafter.

Duplication cysts identified in the children are mostly benign; however, malignant transformation is mainly identified in the older population.[3] Identification of duplication cyst/s in an older individual should lead to a thorough work-up for malignancy.[3] Moreover, it has been reported that malignant transformation is more commonly reported in colonic and rectal duplication cysts than the duplication cysts in other locations.[3] Our patient went into complete remission after rituximab therapy, and the cyst resection surgery was deferred. However, we have kept the child under rigorous follow-up (for symptoms, nutritional assessment and a possible need for repeat imaging).

Girelli et al. (1993) reported an incidence of AIHA in cases of hydatid cysts, who underwent remission after 2 months of mebendazole therapy and the cysts disappeared after three months of therapy.[7] At one step of management of our patient, the cysts were thought to be hydatid cysts, so our patient also received albendazole tablets (15 mg/kg/day) for three months. However, computed tomography (done at admission) did not show any radiological characteristics of hydatid cysts and the cysts did not show any variation in the size (on repeat chest radiograph) after albendazole therapy, suggesting that these cysts were less likely to be hydatid cysts in our patient.

Though there are only a few reports on the possible association between AIHA and duplication cysts, recognition of this rare association requires further studies. It has been reported that secondary AIHA tends to be refractory to steroids and second line therapy is often required in these cases. We recommend that the clinician should consider duplication cysts also as a differential diagnosis, in AIHA patients who require second line agents and investigate accordingly.

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REFERENCES

1. Bennani A, Miry A, Kamaoui I, Harroudi T. Gastric duplication cyst in an adult with autoimmune hemolytic anemia: a case report and review of the literature. J Med Case Rep. 2018;12(1):380.
2. Sangüesa Nebot C, Llorens Salvador R, Carazo Palacios E, Picó Aliaga S, Ibañez Pradas V. Enteric duplication cysts in children: varied presentations, varied imaging findings. Insights Imaging. 2018;9(6):1097–1106.

3. Sreedhar A, Nair R, Scialla W. Paraneoplastic auto-immune hemolytic anemia: An unusual sequela of enteric duplication cyst. Anticancer Res. 2018;38(1):509–512.
4. Liu R, Adler DG. Duplication cysts: Diagnosis, management, and the role of endoscopic ultrasound. Endosc Ultrasound. 2014;3(3):152–160.
5. Wiechowska-Kozłowska A, Wunsch E, Majewski M, Milkiewicz P. Esophageal duplication cysts: endosonographic findings in asymptomatic patients. World J Gastroenterol. 2012;18(11):1270–1272.
6. Tiwari C, Shah H, Waghmare M, Makhija D, Khedkar K. Cysts of gastrointestinal origin in children: varied presentation. Pediatr Gastroenterol Hepatol Nutr. 2017;20(2):94–99.
7. Girelli G, Teggi A, Perrone MP, Di Vico B, Gandolfo GM, De Rosa F. Anti-erythrocyte autoimmunization in hydatid disease. Int J Clin Lab Res. 1993;23(2):113–115.