Neuroblastoma and persistent cloaca are rare yet serious conditions among pediatric patients. To our knowledge, no case of a child born with a cloacal malformation who later developed neuroblastoma has been reported in the medical literature. We present our experience with such patient to report this unique association of two rare medical conditions.

1. Case report

Our patient presented to an outside institution after delivering at 35 weeks gestation. She was noted to have massive abdominal distension, respiratory failure, and signs of intestinal obstruction. Her perineal exam revealed a single orifice consistent with a cloacal malformation. Upon laparotomy, a diverting colostomy was performed along with catheter drainage of the hydrocolpos. A 5 cm common channel cloacal anomaly was subsequently diagnosed (Fig. 1) and the patient underwent definitive repair via a posterior sagittal anorectovaginouterineplasty (PSARVUP) at our institution at two years of age. Following colostomy closure, the patient participated at four years of age in our bowel management program to treat her fecal incontinence. An abdominal radiograph to assess stool burden incidentally revealed an atypical paraspinous opacity over the medial left thoracic base (Fig. 2). This opacity was not seen on previous abdominal radiographs. After noting this finding, we asked the patient and found that she complained of occasional episodes of self-resolved chest pain when playing outside but was otherwise asymptomatic. Additional magnetic resonance imaging was subsequently obtained and delineated a posterior mediastinal mass (7.8 cm × 3.6 cm × 4.8 cm) with extension into the left T10–T11 vertebral foramen, most consistent with neuroblastoma (Fig. 3). Serum catecholamines were within normal limits and there was no evidence of distant disease. A thoracoscopic gross total resection was performed without entering the neural foramina (Fig. 4). Pathology was consistent with poorly differentiated neuroblastoma with unfavorable histology, low MKI, and no N-MYC amplification. Bone marrow biopsy was negative for metastasis. By protocol, the patient is being followed by frequent imaging studies without adjuvant chemotherapy. She is currently six months post-surgery and remains disease free.

This unusual case describes a patient with the unreported combination of neuroblastoma and a complex anorectal malformation.

2. Discussion

To our knowledge, the association of neuroblastoma in a patient born with a persistent cloaca has not been previously described.
The chances of these two conditions occurring together, based on their individual incidences, are approximately 1/200 million [1,2]. While we acknowledge that this case could be the result of random chance, we believe it merits documentation.

Current literature reveals no information concerning an association between these two conditions. Furthermore, it yields minimal understanding of their etiologies. The prevalence of neuroblastoma is one case per 7000–10,000 live births [1]. Though the development of neuroblastoma is not fully understood, evidence indicates that genetic contributions and random mutations play a larger role than environmental exposure [3]. While this is the first case of neuroblastoma associated with cloaca reported in the medical literature to our knowledge, neuroblastoma has been previously reported in association with other conditions including Hirschsprung disease, central hypoventilation syndrome, Beckwith-Wiedemann syndrome, fetal alcohol syndrome, and fetal hydantoin syndrome [1,4].

Persistent cloaca is a congenital malformation in which the rectum, vagina, and urethra fail to separate, resulting in a single common channel. This malformation occurs in about one case in 20,000 live births [2]. The etiology of cloaca and other ano-rectal malformations (ARM) is not fully understood, but research suggests there is a strong genetic component [5]. At this time, a number of genes have been identified as playing a role in the development of ARM [6], though a consensus as to which has the strongest influence has yet to be determined. Cloacal malformations have been associated with a number of urological abnormalities, including

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**Fig. 1.** Three dimensional distal colostogram showing the 5 cm common channel of the cloacal malformation.

**Fig. 2.** Abdominal radiograph revealing the abnormal left paraspinal opacity (arrows) over the medial left thoracic base.

**Fig. 3.** Subsequent MRI better demonstrated the posterior mediastinal mass with imaging features consistent with neuroblastoma. A coronal T1 weighted precontrast image demonstrates the left paraspinal mass (a) and the coronal T1 weighted postcontrast image demonstrates the left neural foraminal invasion (b).
absent kidney, vesicoureteral reflux, horseshoe kidney, ureteral anomalies, and hydronephrosis [7]. However, our review of the medical literature reveals no reported associations of cloaca with a neoplastic process except for presacral mass, which is usually a teratoma [8].

Relevant medical literature offers insight into the relationship of these conditions. In a retrospective study of 538 pediatric neuroblastoma cases, the incidence of congenital genitourinary malformations was significantly increased (OR 5.84) when compared with a similar group of non-cancer patients, though no cloacal malformations were noted [9]. Of more specific relevance, a review of 490 cases of cloaca by Levitt and Pena [7], as well as our center’s subsequent review of an additional 560 cases, also note no associations with neuroblastoma. A retrospective analysis of all ARM in Africa (n = 1401) reported one case (a vestibular fistula in an infant girl) associated with neuroblastoma [10].

Of further interest, aberrant expression of gene EYA1 has been identified in the development of both neuroblastoma and persistent cloaca. EYA1 is a transcription factor of the protein tyrosine phosphatase family and is most notably associated with Branchiootorenal syndrome. During embryologic development, EYA1 forms complexes with SIX proteins, which function as critical regulators of mammalian organogenesis [11]. Evidence has shown that a deficiency in EYA1-SIX1 complexes, specifically in the pericloacal mesenchyme, leads to the development of persistent cloaca [12]. Furthermore, it has been shown that EYA1 is overexpressed in stroma-poor neuroblastoma cells, but not stroma-rich ganglio-neuroblastoma cells [13].

It is therefore tempting to postulate a potential link between these two conditions through an EYA1 gene mutation. For example, it may be the case that a mutated EYA1 protein possesses decreased binding affinity for the SIX1 protein. Simultaneously, low levels of EYA1-SIX1 complexes may lead to compensatory EYA1 overexpression, thereby amplifying EYA1’s SIX1-independent effects on cellular development. Such explanation could account for the development of persistent cloaca (via low EYA1-SIX1 complexes), as well as the development of neuroblastoma (via EYA1 overexpression).

Given the rarity of these two conditions occurring together in the same patient, it is clear that any genetic association is more complex than what we have postulated. We believe, however, that we are in a unique circumstance to have first identified these two conditions in association because of the high volume of anorectal malformation cases seen and followed at our institution. Further studies are needed to elucidate a true genetic link, but awareness of this rare case may serve as a step toward further investigations into these complex pediatric conditions.

3. Conclusion

In conclusion, we present a rare case of a patient born with persistent cloaca who was diagnosed four years later with stage IIA neuroblastoma. To the best of our knowledge, this is the only case in the medical literature in which these two conditions are reported together in the same patient.

Consent

All patient identifying information has been removed form this case to protect anonymity. This study was determined to be exempt by the Cincinnati Children’s Hospital Medical Center IRB.

Conflict of interest

The authors of this case report declare no conflicts of interest.

References