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Case report: Spindle cell neoplasm presenting as a spontaneous intestinal perforation in a term infant

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Spontaneous intestinal perforations in the neonatal population are mostly associated with low birth weight, prematurity, and necrotizing enterocolitis. Spontaneous intestinal perforation in the absence of these risk factors is extremely rare and should raise clinical concern for an underlying bowel pathology. Here we present a unique case of a normal-weight, full-term girl with spontaneous intestinal perforation due to a spindle cell neoplasm with a novel *BRAF* mutation and infantile fibrosarcoma-like morphology. Though rare, malignancy should be considered in the differential diagnosis for bowel perforation in an otherwise healthy, term infant as complete surgical excision can be curative.

KEYWORDS

spindle cell neoplasm, spontaneous intestinal perforation, infantile fibrosarcoma, *BRAF*, neonatal neoplasm

Introduction

We present the unique case of a spontaneous intestinal perforation (SIP) in a normal-weight, term baby girl. Pathology from the bowel segment containing the perforation revealed a *BRAF*-altered spindle cell neoplasm similar in histologic appearance to infantile fibrosarcoma (IFS); however, it lacked the characteristic *ETV6:NTRK3* tyrosine kinase mutation seen in IFS (1). This rare entity of a visceral IFS-like neoplasm without the characteristic mutation has recently been recognized with only 16 cases previously reported in the literature (2–4). Our patient is the second IFS-like neoplasm with described *BRAF* gene rearrangement to present with gastrointestinal disease (5, 6).

Case description

A 3-day-old, full-term baby girl presented at her first pediatrician appointment with decreased appetite, urine output, stool output, and a 14% weight loss since birth. She passed meconium on the first day of life and was breastfed. Her abdomen was noted to be distended and taut with prominent abdominal veins (**Figure 1**).

She had no significant prenatal history. The family history was significant only for breast cancer in a female paternal first cousin in her 4th decade of life and was otherwise unremarkable for malignancy or any intestinal diseases.

Diagnostic assessment

The patient's pediatrician sent the patient to the emergency department where an abdominal X-ray revealed a large volume of pneumoperitoneum concerning for bowel perforation (**Figure 2**). Vital signs were noted to be normal with no fever. Labs were remarkable for a slight leukopenia of 4.75 (normal range: 8.04–15.40) but were otherwise unremarkable. The differential diagnosis included spontaneous intestinal perforation and necrotizing enterocolitis. A surgical consultation was immediately obtained, and the patient was emergently scheduled for abdominal exploration in the operating room.

Therapeutic intervention

An exploratory laparotomy revealed a large perforation in the mid to distal jejunum. Purulence and friable tissue consistent with a subacute presentation of bowel perforation was noted in the abdominal cavity, but there was no evidence of necrotizing enterocolitis or any other intra-abdominal lesions. The segment of the bowel containing the perforation was resected and an enterostomy and mucus fistula were created. Given the degree of gross intra-abdominal contamination due to perforation, a primary anastomosis was not attempted.

Pathology of the resected bowel revealed a perforation measuring 1.4 cm × 0.8 cm in maximum diameter. There was reactive bowel wall thickening around the perforation. A microscopic tumor was identified at the site of the perforation (**Figure 3**). The neoplastic cells were ovoid to spindles with minimal pleomorphism, scattered mitosis (less than 1 per 10 per high power fields), and numerous apoptotic bodies. Neoplastic cells were negative for desmin, smooth muscle actin, MSA, myogenin, myoD1, beta-catenin, CD34, ERG, S100, PHOX2B, NKX2.2, pancytokeratin, CD45, CD68, CD117, ALK, CD1a, and CD207. INI-1 expression was preserved. Ki67 proliferation index was low at 1–2%. There was neoplastic infiltration of the serosa and surrounding adipose tissue, but all surgical resection

margins were free of the tumor with the closest margin at 1 cm. Additionally, no lymphovascular invasion was identified.

The histopathology of the neoplasm resembled IFS; however, a single fusion gene panel did not detect the characteristic *ETV6:NTRK3* fusion transcript associated with IFS. A solid tumor comprehensive panel confirmed this result and additionally revealed two distinct mutations in *BRAF*: the first, a missense mutation of lysine to arginine in exon 15; and the second, a novel exon 1-11 variant splicing consistent with the intragenic deletion of exons 2-10. With this genetic profile, the tumor was classified as a *BRAF*-altered spindle cell neoplasm with IFS-like morphology and non-specific immunoprofile containing a novel *BRAF* mutation.

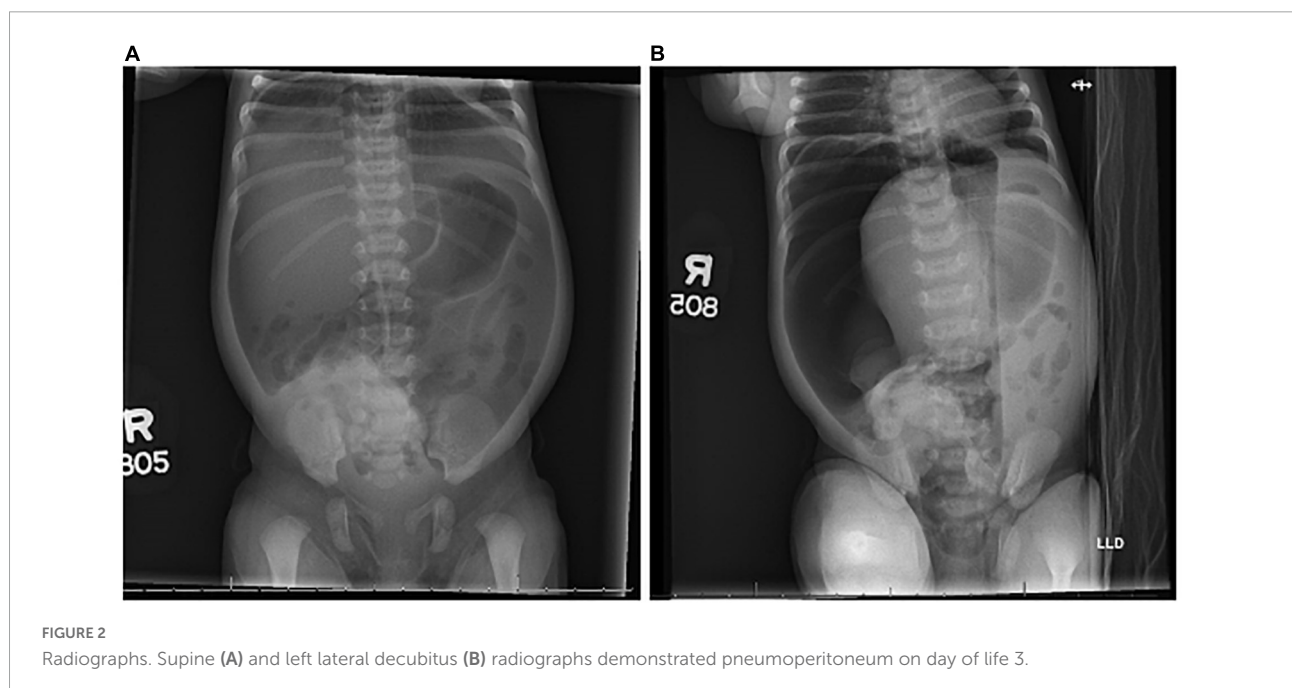
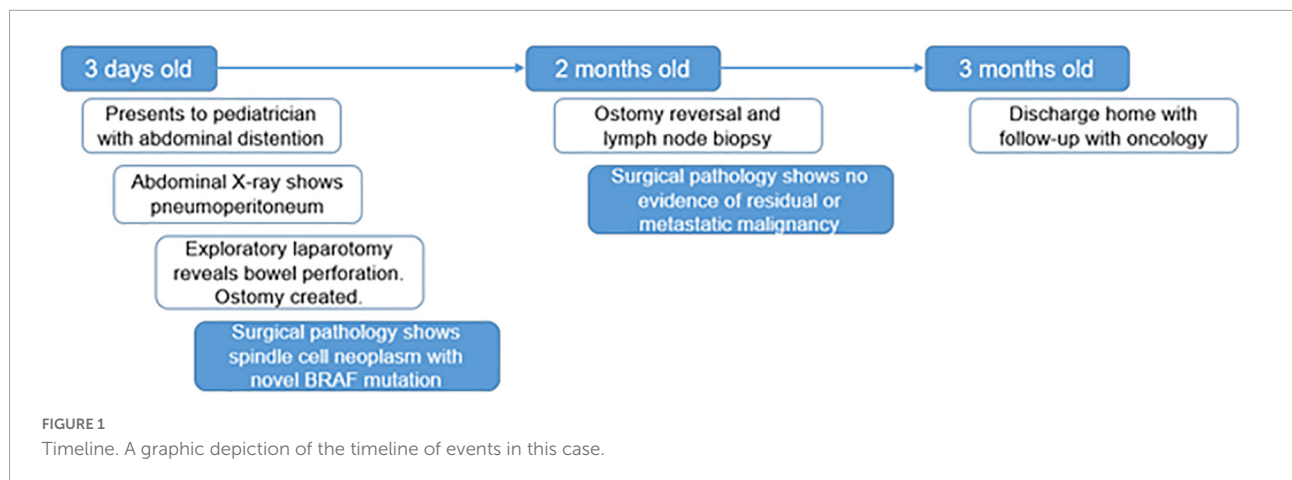
Follow-up and outcomes

Following the diagnosis of neoplasm, a CT scan of the chest, abdomen, and pelvis was obtained to look for other sites of disease. This revealed sub-centimeter soft tissue nodules on the anterior chest and abdominal wall, but no evidence of distant disease. The patient had an ostomy reversal about 2 months after her initial laparotomy. A soft tissue nodule adjacent to the surgical incision was biopsied and showed signs of benign fibromuscular tissue with reactive changes but no malignancy. One of the radiographically identified anterior chest soft tissue nodules was biopsied at this time and pathology also revealed no evidence of malignancy or pathologic abnormality.

Based on the available literature, a primary resection with negative margins was determined to be the only necessary treatment and no adjuvant treatment was planned. The patient was followed with routine imaging and physical exams. The genetic evaluation showed no germline *BRAF* mutation and no *BRAF*-associated genetic syndromes. The patient was discharged home at 3 months of age and is currently thriving with no signs of disease recurrence.

Discussion

Spindle cell neoplasms are a rare form of soft tissue neoplasms that were previously classified based on morphology. In the last decade, molecular oncology and immunohistochemistry have allowed this broad and unspecific notation of tumors to be subclassified into groups based on molecular signatures (7, 8). One of these pediatric subclassifications is IFS, which is most often found in the limbs of children in their first year of life (4, 9). This tumor is characterized by the molecular signature of an *ETV6:NTRK3* translocation that affects a tyrosine kinase (1, 6). While our patient's tumor had a similar morphology to IFS, it lacked this molecular signature. However, recent studies have shown a subset of IFS-like lesions affected by related kinase mutations



show a higher inclination toward visceral tumors in neonates (2–4, 10). Similar to this small subset of patients previously described in the literature, our patient presented in the few days of life with unexplained intestinal perforation. Unlike other cases previously described, our patient did not have a discrete tumor evident on laparotomy. *BRAF* gene fusion in an IFS-like neoplasm has been described in a small group of patients (5), but only once before in a visceral tumor (6).

The proto-oncogene *BRAF* codes for a serine/threonine kinase within the regulation of the MAPK/ERK signaling pathway and is vital for cell division and differentiation (11). Mutations in *BRAF* are one of the most prevalent mutations, seen in a wide variety of cancers, but only in <0.6% of soft tissue cancers (11–13). Though the large majority (80%) of *BRAF* mutation occurs at the V600 position, our patient presented with

lysine to arginine substitution at the K601 position (K601N), which makes up only 7.5–11% of non-V600 *BRAF*-associated tumors. In two prior studies, this mutation has been shown to confer gain-of-function to the kinase portion of the *BRAF* gene and increases cell proliferation (11, 13, 14).

In addition to the K601 mutation, our patient also possessed a novel *BRAF* mutation of exon 1-11 variant splicing consistent with the intragenic deletion of exons 2-10 (Figure 4). This mutation is predicted to affect the kinase's inhibitory autoregulation mechanism while still maintaining the ability to dimerize and activate normally (15, 16). This mutation eliminates two major conserved regions of the protein (CR1 and CR2) (Figure 4). CR1 contains the Ras binding domain (RBD) and the cysteine-rich domain (CRD) which are located in the general areas of exons 3-6 and exon 8, respectively (11). This

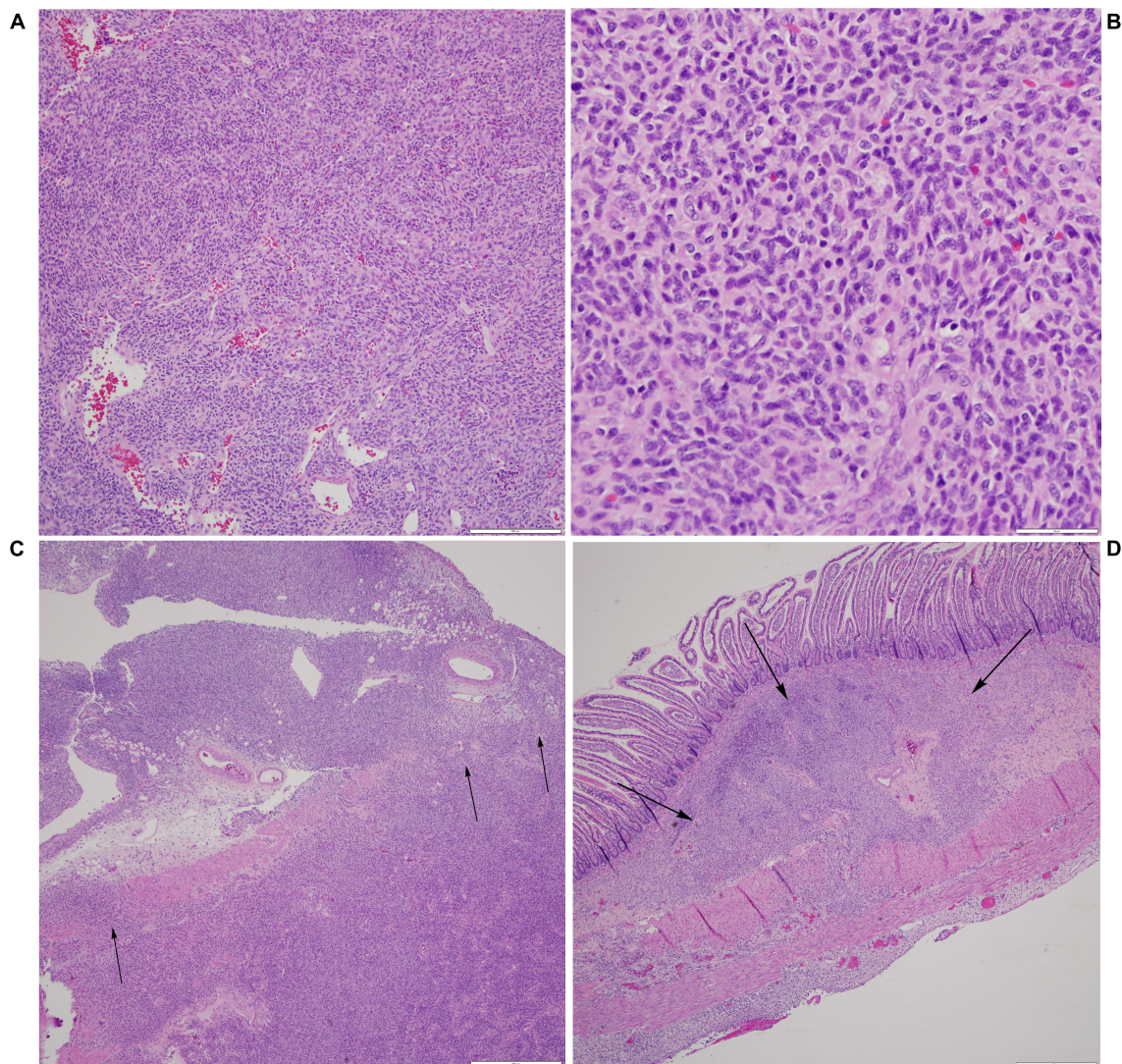
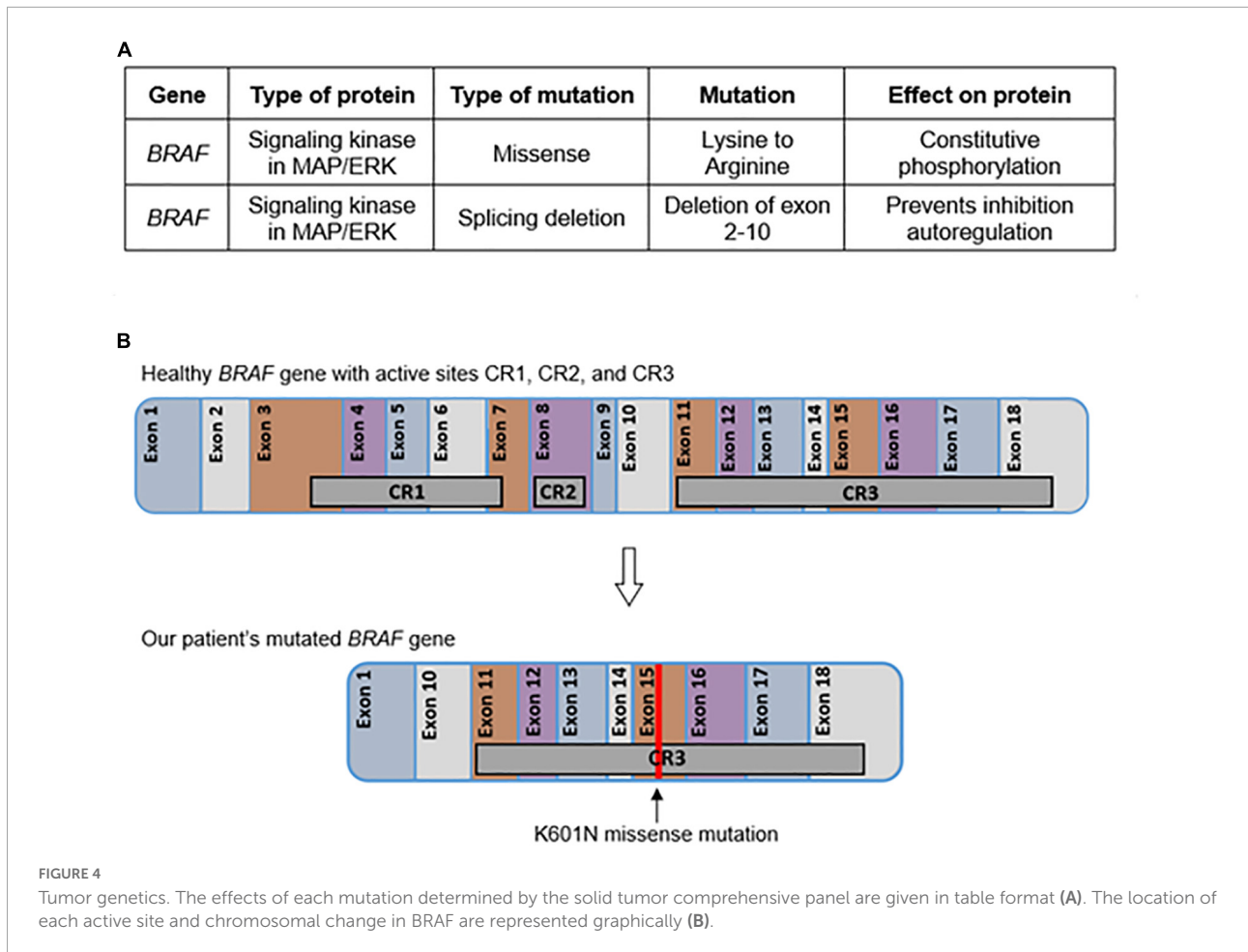


FIGURE 3

Histological examination of neoplasm. **(A)** Prominent vasculature is identified within some areas of the spindle cell neoplasm, with several vessels demonstrating a staghorn-like appearance (H&E, scale bar is 200 microns). **(B)** At higher power, the neoplastic cells are monomorphic, ovoid to spindle, with a moderate amount of cytoplasm and coarse chromatin, and scattered apoptotic bodies are noted (H&E, scale bar is 50 microns). **(C)** At the site of perforation, the neoplastic cells are seen infiltrating through the muscularis propria and into the serosa and surrounding fibroadipose tissue (H&E, scale bar is 500 microns). **(D)** These nests of neoplastic cells are away from the main site of perforation and are identified as percolating through the submucosa (H&E, scale bar is 500 microns).

area of the kinase has been shown *in vitro* to play a major role in the cell's intrinsic ability to inhibit and control the activation of the MAPK/ERK pathway (17). In a functioning *BRAF* kinase, the activated Ras protein binds to the RBD and CRD to activate the kinase cascade. The splice mutation in our patient eliminates RBD and CRD and allows uninhibited activation of cascades such as the MYC, VEGF, ITGB3, and MDMD2 pathways, all of which are associated with oncogenesis. Additionally, loss of CR2 leads to loss of another route of inhibition on the *BRAF* kinase (11). This combination of mutations has not been previously described in the literature.

Mutations in *BRAF*, specifically at the K601 location, have been previously associated with a classification of germline diseases called RASopathies (17). These diseases are caused by a variety of germline pathogenic mutations within genes of the RAS/MAPK pathway and produce phenotypically similar presentations of variations of craniofacial abnormalities, epilepsy, short stature, intellectual and motor developmental delay, and cardiac abnormalities (18). Compared to other RASopathies, *BRAF*-associated cases have a higher prevalence of intellectual development delay and epilepsy. Most notably, one concerning factor of RASopathies is the higher prevalence



of neoplasm, especially with mutations that are associated with oncogenesis, such as K601 (17, 18). While our patient did not present with evidence of germline *BRAF* mutation or any RASopathy-associated phenotypic features, this group of pathologies must be considered in patients presenting with a *BRAF* mutation.

Our patient's novel *BRAF*-associated malignancy presented as SIP. Though well-documented in neonates of low birth weight, SIP is rarely seen in normal weight, full-term neonates. In the low-birth-weight neonate, intestinal perforation may occur in the presence of necrotizing enterocolitis (NEC) and is associated with high mortality and morbidity (19, 20). Risk factors include indomethacin, steroids, and maternal chorioamnionitis (21, 22). In the term neonate, intestinal perforation is associated with underlying pathologies such as Hirschsprung disease or cystic fibrosis (23, 24). SIP due to neoplasia is extremely rare in the neonatal population, yet recent case series suggest a group of intestinal IFS-type tumors may present with early, acute onset SIP in otherwise healthy infants (2–4, 10). IFS most often presents in the distal extremities in older infants, while cases affecting the gastrointestinal tract make up only 10% of cases and

present mainly in neonates (3, 4, 9). Recognition of this clinical presentation is vital as our patient did not have any indication of a mass-forming lesion, which may have led to the incorrect exclusion of malignancy. Diagnosing the correct etiology of the perforation may be lifesaving as a complete surgical excision has been curative in similar cases associated with IFS or an IFS-type tumor (2, 6). Favorable prognoses have been reported with no recurrences at a 5-year follow-up (2).

Novel *ETV6:NTRK3* fusion negative, IFS-like spindle cell neoplasms have recently been recognized as a cause of early, acute onset SIP in otherwise healthy infants (2, 4). Our patient experience highlights the importance of recognizing this rare, but significant, the clinical entity in the full-term infant who presents with SIP.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

LTC and LSC were the primary authors of the manuscript. AL and NQ contributed to the **Figure 3** and provided expertise on tumor pathology and genetics. JHF provided the oncologic expertise. CG provided the expertise in neonatology. TCL provided the expertise in the surgical management of the

patient. EAO and RMB contributed to the literature review. All authors reviewed and edited the final manuscript and figures.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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