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CASE REPORT

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Sudan black poisoning resulted in methemoglobinemia in a baby with congenital chyloperitoneum

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Key Clinical Message

Treatment of congenital chyloperitoneum is a challenge. Conservative methods may be ineffective. Preoperative visualization of the site of lymphatic leakage is crucial, but radiological imaging is technically complicated and may not provide sufficient information, especially in small patients. To ease the detection of lymphatic leakage during surgery, preoperative feeding with fat-rich formula with Sudan Black has been recommended. However, administration of Sudan Black may result in life-threatening methemoglobinemia and liver damage without any advantage of revealing leakage during surgery. We recommend preoperative feeding with pure fat-rich formula.

KEYWORDS

congenital chyloperitoneum, methemoglobin, octreotide, propranolol, Sudan black, Sudan red

1 | INTRODUCTION

Congenital chyloperitoneum (CC) is a rare condition with etiology which often remains unrevealed. In these cases, malformations of lymphatic system are considered to be the most likely underlying disorder.[1] The aim of conservative treatment is to reduce lymph production and alleviate the high daily protein and fluid loss. When no or little effect of conservative methods is achieved, surgical treatment remains an option. Detection of the site of lymphatic leakage preoperatively is a key issue for successful surgery. Successful lymphoscintigraphy or MR lymphangiography in very young patients is a real challenge. Even open surgery may not reveal the exact location of leakage.[2] Therefore, preoperative feeding with a fat-rich formula and lipophilic dyes are recommended in literature to ease detection of the leakage and increase the likelihood of successful surgery.[2–5] Sudan B (black) and Sudan III (red) are these fat-soluble dyes which have been used for the detection of lymphatic leakage. Sudan dyes are synthetic azo dyes which contain characteristic N=N compound. These dyes are used industrially as coloring agents, and their usage is regulated by environmental laws and usage in food products is not allowed.[6]

We present a case of the use of Sudan B for visualization of leakage in CC complicated by methemoglobinemia.

2 | CASE HISTORY

A girl with birthweight of 3255 g was born via cesarean section at a gestational age of 32 weeks with extremely large abdomen (Figure 1). Apgar score was 4, 7, and 7 at 1st, 5th, and 10th minutes, respectively. The baby needed

immediate respiratory support with Neopuff due to irregular breathing. After initial stabilization her breathing and oxygenation were satisfactory at CPAP 5 cmH_2O and FiO_2 of 40%. Blood pressure was within normal range.

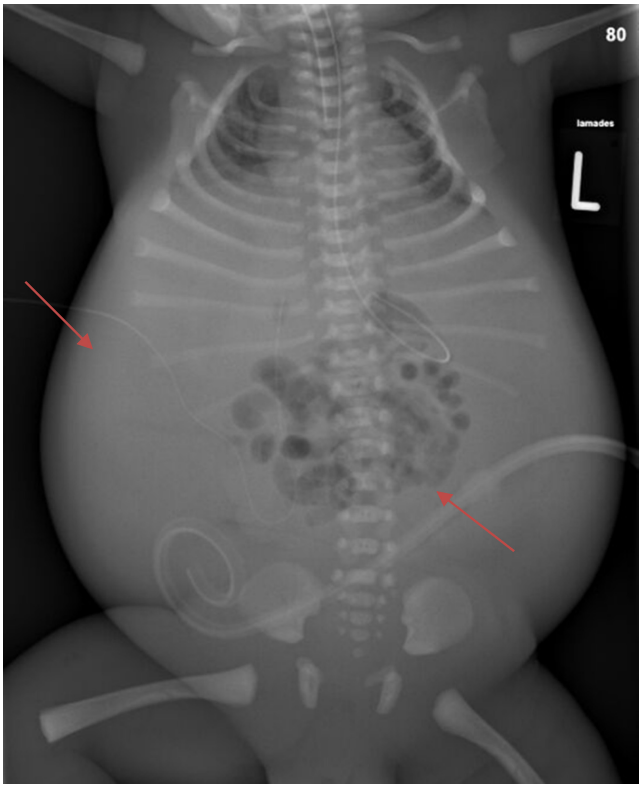

FIGURE 1 X-ray on the first day. Congenital ascites. Grossly distended abdomen (upper arrow). The gas-filled upper bowel loops appear to be centrally displaced (lower arrow). No body-wall edema.

3 | METHODS

Abdominal ultrasonography (US) revealed massive ascites, empty intestines without peristalsis and prominent cisterna chyli with no other abnormalities of the abdominal organs. Brain ultrasound revealed mild asymmetry of the frontal horns of lateral ventricles. Echocardiography was normal. She had leukopenia thrombocytopenia and coagulopathy in laboratory tests at birth (Table 1). She was intubated for placement of peritoneal catheter. The amount of drainage was 1124 mL during the first 24 h. White blood cells in peritoneal fluid were mainly lymphocytes and triglycerides were low before enteral feeding with Aptamil Prematil (Table 1). CC was diagnosed when leakage turned milky, and triglycerides increased in peritoneal fluid (Table 1). Feeding with MCT (medium chain triglycerides) formula was started. Abdominal MR lymphangiography at the 13th day of life (body weight of 2300 g) failed to detect the site of lymphatic leakage. At 15th day of life octreotide treatment was started and increased slowly up to 10 μg/kg/h. The amount of leakage persisted around 130–280 mL/24 h (Figure 2) regardless of the amount of enteral feeds (daily amount of MCT formula varied from nil per os (NPO) to 25 mL/kg/day). Titration of octreotide infusion up to 20 μg/kg/h together with NPO was tried without any effect. At the age of 2 months and 17 days, propranolol was added (Figure 2) and titrated up to 6 mg/kg/day. No effect was seen within 8 weeks. Long-term parenteral feeding

TABLE 1 Laboratory tests.

		Peritoneal fluid	
	Blood tests at birth	**At birth**	**With formula feeding**
Leukocytes	4.1×10^9/L	2762 E6/L	7307×10^6/L
Neutrophils	1.84×10^9/L	Lymphocytes 91,5%	Lymphocytes 81,5%
Lymphocytes	0.41×10^9/L		
Monocytes	0.42×10^9/L		
Erythrocytes	Within normal limits	$32{,}000\times10^6$/L	$37{,}000\times10^6$/L
Thrombocytes	95×10^9/L		
INR	1.9		
PT	30%		
D-dimers	19.85 mg/L		
Fibrinogen	0.93 g/L		
AT III	27%		
Albumin		18 g/L	
Protein		21 g/L	35 g/L
Triglycerides		<0.1 mmol/L	0.85 mmol/L

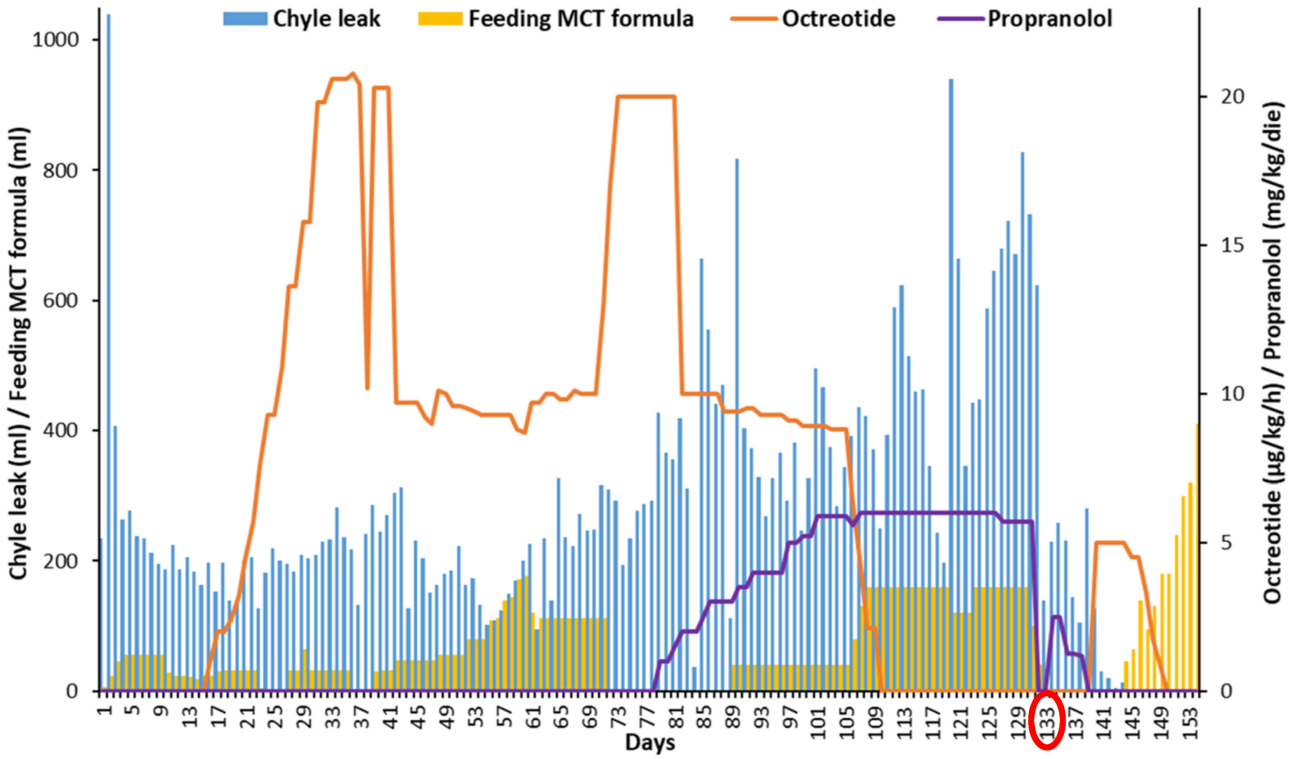

FIGURE 2 Conservative treatment time course: restricted enteral feeding with medium chain triglycerides, octreotide infusion, propranolol per os. Day of surgery marked as red oval.

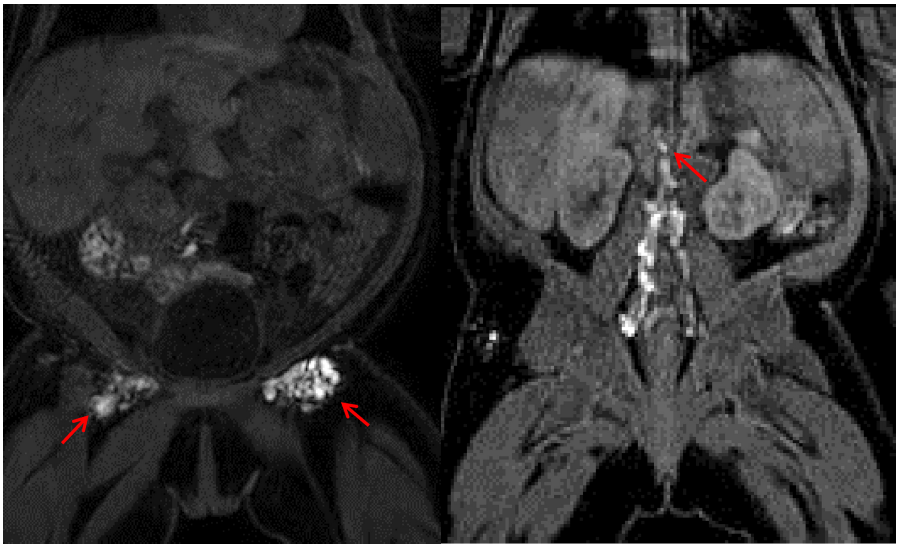

FIGURE 3 MR Lymphography 3D T1-weighted images. Injected contrast agent in inguinal area (on the left, arrows) at 3 min and in retroperitoneal lymphatic channel up to cisterna chyli (on the right, small arrow) at 12 min after injection.

resulted in mild parenteral nutrition-associated liver disease (PNALD) with elevated bilirubin (max 204 µmol/L), aspartate aminotransferase and alanine aminotransferase (max 421 and 239 U/L, respectively). Ursodeoxycholic acid and fish oil triglycerides emulsion together with medium chain triglycerides enteral feeds providing 20% of total calories were used to alleviate symptoms.

At the age of 4 months and 10 days, at body weight of 6280 g, repeated abdominal MR lymphangiography demonstrated collections of injected contrast agent in inguinal area and in retroperitoneal lymphatic channel, where it stopped at the level of cisterna chyli (Figure 3). Exploratory laparotomy was performed. Fat-rich formula with 1.6 g of Sudan Black was given pre-operatively to ease identification of the location of lymphatic leakage.[4] During the operation the dye failed to reveal the site of leakage, the lymphatics were better visualized because of the fat-rich formula. A large lymph node of 2.5 × 1 cm

between common bile duct and duodenum, reaching to retroduodenal area, was ligated at both sides and additional ligatures were placed at para-aortic area behind pancreas, to the place, where accumulation of milky liquid was seen. The area was covered with fibrin glue. Postoperatively, the baby's complexion become grayish. Blood sample 16 h after the first administration of Sudan Black showed significantly increased methemoglobin (from 1.7% preoperatively to 15.8% within 6 h from surgery). The baby was treated with methylene blue. Methemoglobinemia resolved within an hour (Figure 4). Postoperatively, a 2-3-fold increase from preoperative level in ALT, AST and bilirubin values was noted with a decrease to preoperative level from the second postoperative day. The amount of chyle leakage decreased gradually after surgery and enteral feeding with MCT was started on 11th and full enteral feeding reached on 35th postoperative day (Figure 2).

4 | RESULTS

Treatment of CC remains challenging. When all conservative methods prove ineffective, surgery may offer a life-saving alternative. Visualizing the exact site of chyle leakage with radiological imaging may be helpful when preparing for surgical intervention. In very small and very young patients repeated attempts with detailed planning may eventually provide required information. Preoperative feeding may help to discover the exact place of leakage and to close definitively the leakage during surgery.

5 | DISCUSSION

We describe a case of methemoglobinemia after Sudan B administration in an infant with CC refractory to conservative treatment. Although the use of Sudan dyes has been suggested to visualize lymphatic leakage to improve success of surgical interventions, very limited data/only a few case reports describe the outcomes.[2–5] There is no description of short- and long-term risks related to the administration of Sudan dyes to infants or children. Very little is known about the toxicity of Sudan dyes generally. Azo compounds (including Sudan dyes) are regulated in food industry due to their potential to cause of mutagenic, teratogenic, genotoxic, carcinogenic, and epigenetic effects.[6] These effects are associated with Sudan dyes and its metabolites, especially

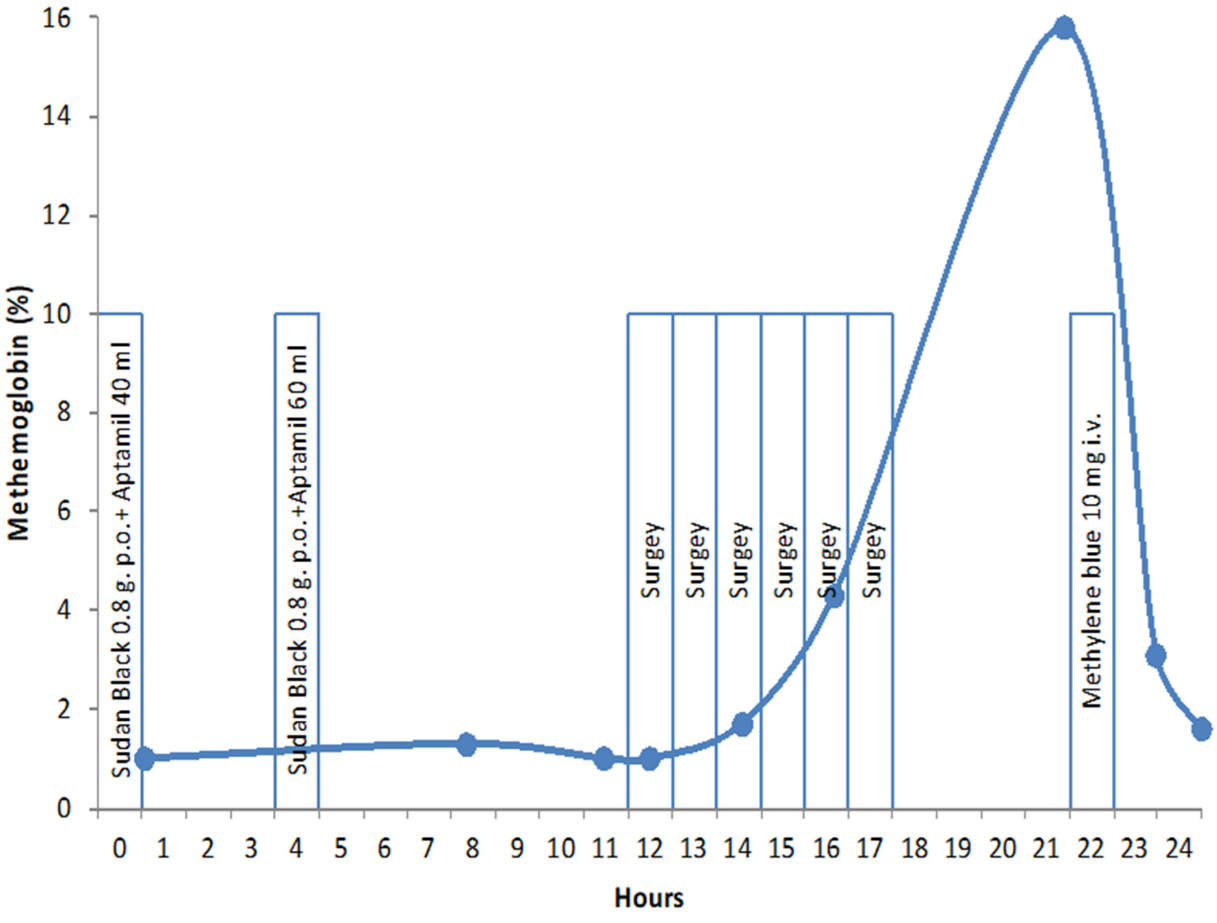

FIGURE 4 Day of surgery and methemoglobinemia.

aromatic amines, generated during metabolism in liver and during degrading process by microbes of human skin and gastrointestinal tract. Exact molecular mechanisms behind these toxic effects are not known.[6] Sudan Black and Sudan Red, both used to locate lymphatic leakage, are grouped as "not classifiable" by the International Agency for Research.[6,7] This means that insufficient human and animal data are available. Sudan Black B is considered to be harmful to skin and toxic to mucus membranes.[7] Sudan dyes may destroy balance of intestinal microbiota and may lead to additional health risks.[8]

Our experience shows that Sudan dyes may dispose small patients into risk of methemoglobinemia, although no firm conclusion can be drawn based on a single case. The administered dose resulted in a potentially life-threatening situation, requiring emergency intervention, in our case. There are no certain guidelines about dosage of Sudan dyes in case of CC. We used a similar dose as proposed by Mouravas V et al. The peak of methemoglobin concentration was probably higher than that measured an hour before methylene blue treatment. Signs of methemoglobinemia depend on hemoglobin level and are aggravated by low hemoglobin levels and accompanying heart, lung, and hematological disorders.[9] Low hemoglobin level is not uncommon during surgery and makes the situation particularly dangerous. In addition, it is almost impossible to notice the appearance of neurological symptoms during surgery or in the immediate postoperative period.

Kola-Ajibade et al. observed a significant increase of liver enzyme aminotransferase, alkaline phosphatase activity and bilirubin and lower albumin levels in rats after ingestion of 50 mg/kg of Sudan II and IV with palm oil.[10] A study by Elham et al. demonstrated a significant reduction in hematological parameters, such as total leukocyte and erythrocyte count, hemoglobin content, and hematocrit percentage, after administration of Sudan II to rabbits.[11] The effects of azo compounds to hematological parameters, including lysis of blood cells, hemolytic anemia and methemoglobinemia, can be explained by cytochrome P450 metabolism of Sudan dyes.[12] A common metabolic pathway of Sudan dyes through azo bond reduction in p-aminoazobenzene leads to the formation aryl hydroxylamines.[13] The role of these aromatic amines in methemoglobin formation has been noted in several studies.[14,15] For example, aniline is known to cause methemoglobinemia through action of its strongly oxidizing metabolites.[14,16–18]

Moreover, several other highly reactive compounds such as superoxide from semiquinone radicals, hydroxyl radicals, or hydrogen peroxide are formed through metabolism of azo compounds.[19] These reactive oxygen species cause the lysis of red blood cells through crosslinking adjacent proteins.[10]

We did not see any advantage of administrated Sudan Black during the operation. The milky lymphatic secretion would have been as well distinguishable from other secretions as was the slightly greenish color achieved with added Sudan Black.

Our case also demonstrates that the recently recommended high dose octreotide as well as propranolol are well tolerated, but not always effective, even if enteral feeding is stopped. While Octreotide is often recommended with titration up to a maximum dose of 12 μg/kg/h, in some CC cases infusion of 20 μg/kg/h has proven effective.[20,21] Although pulmonary hypertension[20] and necrotic enterocolitis[22] are reported side effects, octreotide has been generally well tolerated by neonates.[21,23] K. Mitchell et al. described four neonates with chylous effusions, effectively treated with propranolol dose up to 6 mg/kg/die.[24] Effect was seen within a couple of weeks in these patients. In our case, propranolol treatment failed to show any effect. Leakage rather increased as the baby grew.

Due to toxicity of Sudan dyes we rather recommend preoperative use of fat-rich formula only to improve visualization of the leakage during surgery. Administration of Sudan Black may result in life-threatening methemoglobinemia and cause additional liver damage, especially in babies with long-term parenteral feeding.

6 | CONCLUSION

This patient is by now 2.5 years old. No recurrence of chyloperitoneum has been occurred and she can eat normal food. She needs physiotherapy due to mild developmental delay.

AUTHOR CONTRIBUTIONS

Helgi Padari: Conceptualization; data curation; writing – original draft; writing – review and editing. **Karin Kipper:** Conceptualization; supervision; writing – original draft. **Imbi Eelmäe:** Writing – original draft; writing – review and editing. **Jekaterina Nerman:** Writing – original draft. **Mare Lintrop:** Writing – original draft. **Tuuli Metsvaht:** Conceptualization; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Authors do not have any conflict of interest to declare concerning the matter of the article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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