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Chromosome 4q28.3q32.3 duplication in a patient with lymphatic malformations, craniosynostosis, and dysmorphic features

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Short clinical summary

The proband, now a 4-year-old female of mixed Caucasian and Japanese ancestry, was born at 29 weeks gestation via spontaneous vaginal delivery following a pregnancy complicated by fetal ascites, echogenic bowel, polyhydramnios, and incompetent cervix. The mother had no other pregnancy complications and had no recognized teratogen exposures throughout the pregnancy. Her length was 37 cm (37^{th} centile), weight was 1.478 kg (80^{th} centile), and occipitofrontal circumference (OFC) was 27 cm (20^{th} centile). The family history was significant for maternal family members with pregnancy losses of unknown etiology: one each for the mother and maternal grandmother. The great maternal grandmother reported at least 4 or 5 pregnancy losses. Consanguinity was denied.

The proband remained in the neonatal intensive care unit for the next 8 months for management of severe respiratory issues, ascites and feeding difficulties. During that time, she underwent placement of a tracheostomy, a Denver (peritoneovenous) shunt for ascitic-fluid drainage, an intravenous port and a gastrostomy tube for feeds (Fig. 1). Additional pertinent findings then include retinopathy of prematurity, subglottal stenosis grade IV, hypothyroidism, 11 sets of ribs, mild bilateral hydronephrosis, accessory spleen and persistent ascites (Fig. 2).

At 20 months dysmorphologic evaluation was significant for macrocephaly, open anterior and posterior fontanelles, bicoronal craniosynostosis on CT scan, right posterior plagiocephaly, brachycephaly, cupped and prominent ears with hypoplastic antihelices, broad forehead, a short

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Conflicts of interest

The authors have no conflicts of interest to disclose

and upturned nose, telecanthus, ocular hypertelorism, depressed nasal bridge (Figure 3A–B), moderate ascites, bilateral overriding of the second and fourth toes over the third toe, short stature and hypotonia. At this latter time, she exhibited significant developmental delays; she was unable to sit unassisted or feed herself. However, she was able to crawl, pull to a stand and sit independently. The proband could feed herself but still required a G-tube for much of her nutrition. She was nonverbal but able to use 12 signs. She continued to require a tracheostomy but only for night-time mechanical ventilation. At 33 months when last evaluated, her height was 79.2 cm (<1st centile), weight was 11.6 kg (7th centile) and OFC was 56 cm (>97th centile).

The patient's severe ascites persisted throughout the first 2 years of her life. At age 22 months, she underwent lymphatic imaging at the Children's Hospital of Philadelphia that revealed multiple dilated perihepatic lymphatic vessels and leakage of contrast material into the peritoneum (Fig. 4A–D). Subsequently, she underwent successful embolization of these lymphatic vessels with resolution of her ascites.

Keywords

Lymphatic malformations; Congenital ascites; Bicoronal craniosynostosis; Developmental delay; Growth failure; Ocular hypertelorism; Upturned nose

Investigations

Prenatally, the patient's mother was closely monitored following a previous loss associated with incompetent cervix. Prenatal ultrasound examinations at 11, 12, 15, and 19 weeks were normal. At 24 weeks gestation, the ultrasound examination found the abdominal circumference at the 95th centile and fetal ascites. At 26 weeks the examination revealed persistent fetal ascites and echogenic bowel. At 28 weeks polyhydramnios was also present. An integrated maternal serum screen indicated an increased risk for Down syndrome (>1:10) but cell-free fetal DNA testing showed no increased risk for trisomy 13, 18 or 21.

At 26 weeks gestation, the mother had an amniocentesis for prenatal genetic diagnosis. G-banded chromosome analysis identified a duplication of genetic material on chromosome 4 [46,XX,add(4)(q35.1)]. A SNP microarray revealed a gain of 28.84 Mb at 4q28.3q32.3. The break points were reported at coordinates 131,317,569 to 168,722,292 based on the NCBI Human Genome Build 37 (hg19). Karyotypes of both parents were normal. TORCH titer analyses revealed no evidence of congenital infection.

At 6 months of age, the proband underwent gene testing with a 23-gene RASopathy panel and a 74-gene lysosomal storage disease panel, both of which were negative. Whole exome sequencing subsequently found no pathogenic variants or variants of uncertain clinical significance. She underwent whole genome sequencing through the iHope program from Illumina Biosciences, which only reported the aforementioned chromosome 4q28.3q32.3 duplication. Ultimately, she underwent RNA sequencing which was largely unrevealing.

She did not have a complete skeletal survey. However, her chest and abdominal radiographs showing the ribs, vertebrae, humeri and pelvis, all had normal bone structures. We think that is is unlikely that she has a bone dysplasia.

At 3 months of age, inguinal and pelvic lymphography demonstrated lymph drainage caudally toward her legs and away from the abdominal cavity with minimal abdominal drainage. At age 22 months, dynamic contrast magnetic resonance lymphangiography (DCMRL) demonstrated intact cisterna chyli and normal drainage to the thoracic duct. This was followed by transhepatic lymphangiography that revealed multiple dilated perihepatic lymphatic vessels and leakage of contrast to the peritoneum (Fig. 4A–D).

Discussion

We present a 4-year-old female with a complicated medical history and multiple abnormal findings. Her major abnormalities include bicoronal craniosynostosis, lymphatic abnormalities associated with severe ascites, and a 4q28.34q32.3 chromosome duplication. We cannot find that her pattern of anomalies has been described before in association with chromosome 4q duplications or any other syndrome.

It is possible that some aspects of our patient's presentation are consistent with known manifestations of chromosome 4q duplication including some dysmorphic features, craniosynostosis, and developmental delay (Lundin et al., 2002; Thapa et al., 2014). However, many of her physical findings are more severe or have not been reported in chromosome 4q duplications. Further, our patient does not exhibit microcephaly, significant congenital heart disease, or the digital anomalies noted in other published cases of chromosome 4q duplications (Lundin et al., 2002).

The duplication in our patient contains 329 genes (87 annotated in OMIM). We have evaluated all 87 OMIM genes and to our knowledge, none is involved with lymphatic development. Moreover, neither whole exome sequencing nor whole genome sequencing identified any pathogenic mutations in other genes.

One of the unique features of our patient is the development of perihepatic dilated lymphatic vessels causing marked and chronic ascites. We did not identify a germline cause for the lymphatic malformation. These lymphatic findings do not fit into any of the recognized lymphatic syndromes of which we are aware including Hennekam lymphangiectasia (Hennekam et al., 1989), Perlman syndrome (Alessandri et al., 2008), Klippel-Trenaunay syndrome (Oduber et al., 2008), Parkes Weber syndrome and yellow nail syndrome (Duhra et al., 1985). Ascites has also been reported in Noonan syndrome (Schlüter et al., 2005), Turner syndrome (Wax et al., 1992), lysosomal storage diseases (Staretz-Chacham et al., 2009), and mutations in the *ITGA9* gene (Ma et al., 2008). Again, she does not appear to have clinical histories or genetic testing results consistent with any of those disorders.

We did not identify a germline cause for the lymphatic malformation. However, We did consider a somatic etiology for the lymphatic malformation. The infant did not have any epidermal nevi and we do not have any tissue from the lymphatic malformation to sequence. Of further note, we report the successful use of DCMRL to diagnose our patient's

intraabdominal lymphatic abnormalities and the successful use of embolization to treat these lymphatic defects.

We propose that the patient presented here has a previously unrecognized dysmorphic syndrome with bicoronal craniosynostosis, congenital abnormality of the lymphatic system and multiple other findings. While her chromosome 4q duplication likely contributes to her phenotype, we suspect that she is affected by a separate syndrome of unknown etiology. Extensive genetic evaluation has found no definite diagnosis accounting for her findings.

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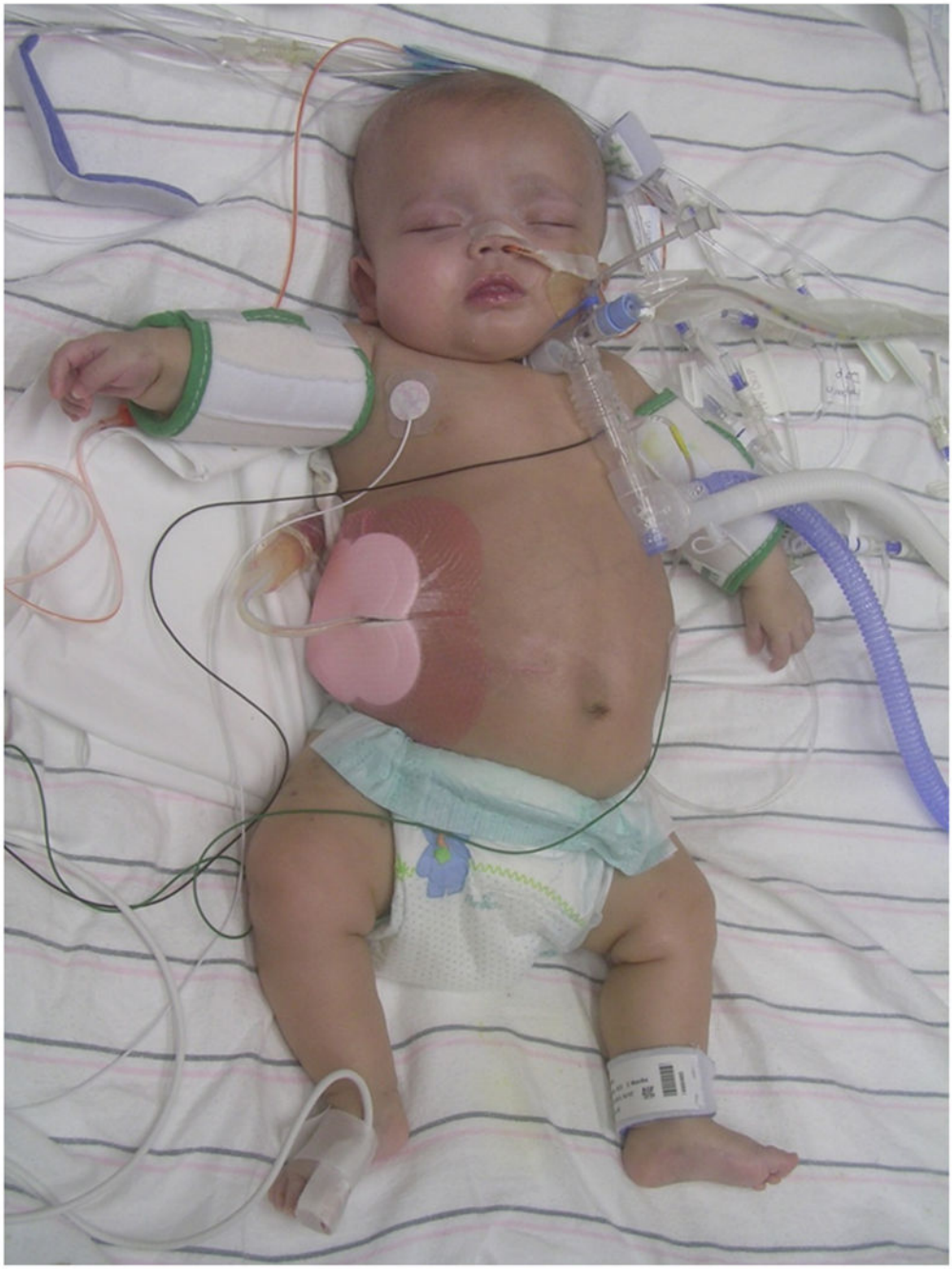

Figure 1:
The patient at age 6 months of age. Note the tracheostomy and tubing connected to her neck, the peritoneal drain on her abdomen, the distended appearance of her abdomen and no significant extremity edema.

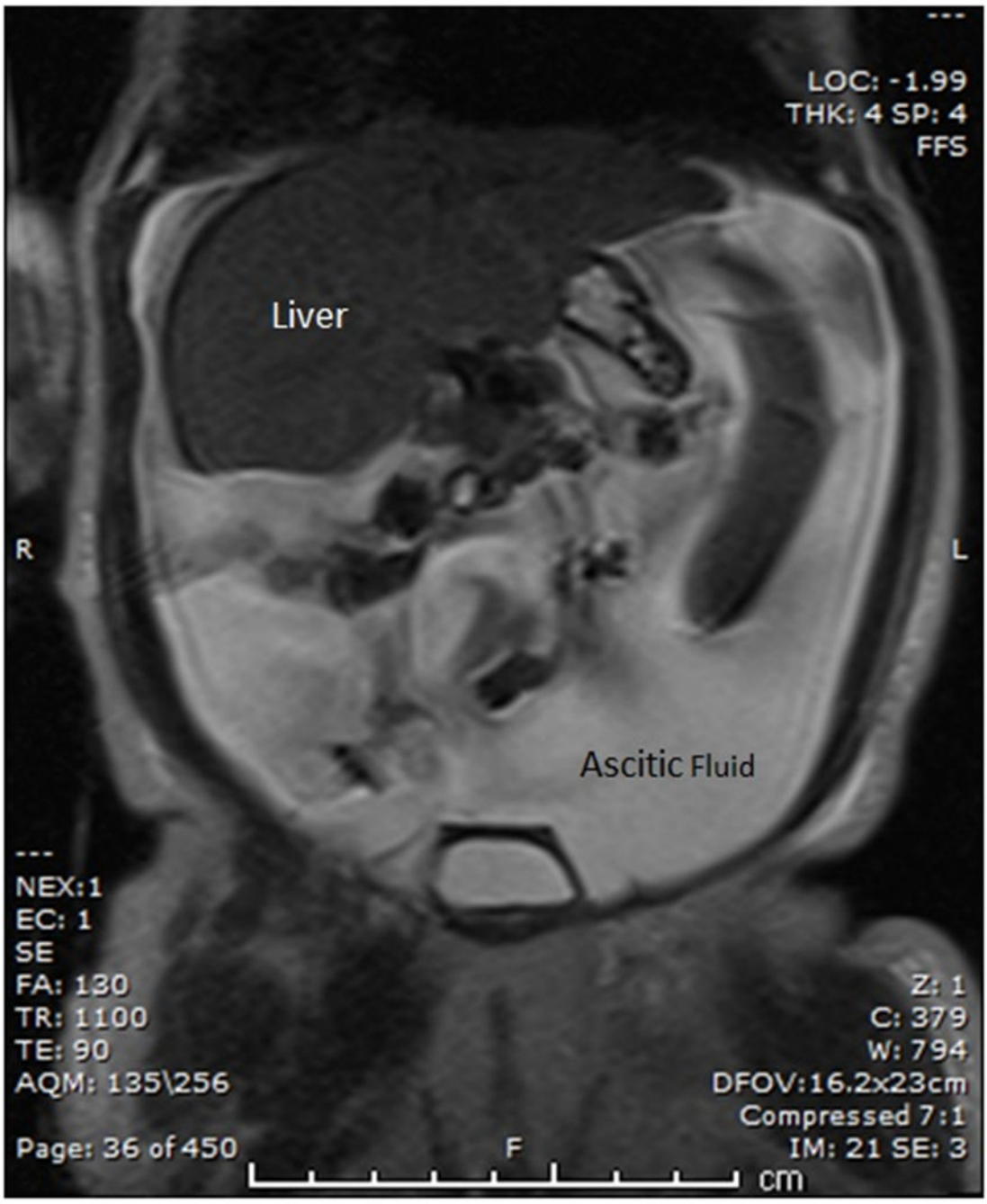

Figure 2:
T2-weighted MRI of the patient's abdomen at 3 months of age. Note the presence of ascitic fluid in the peritoneal cavity that appears as a bright substance.

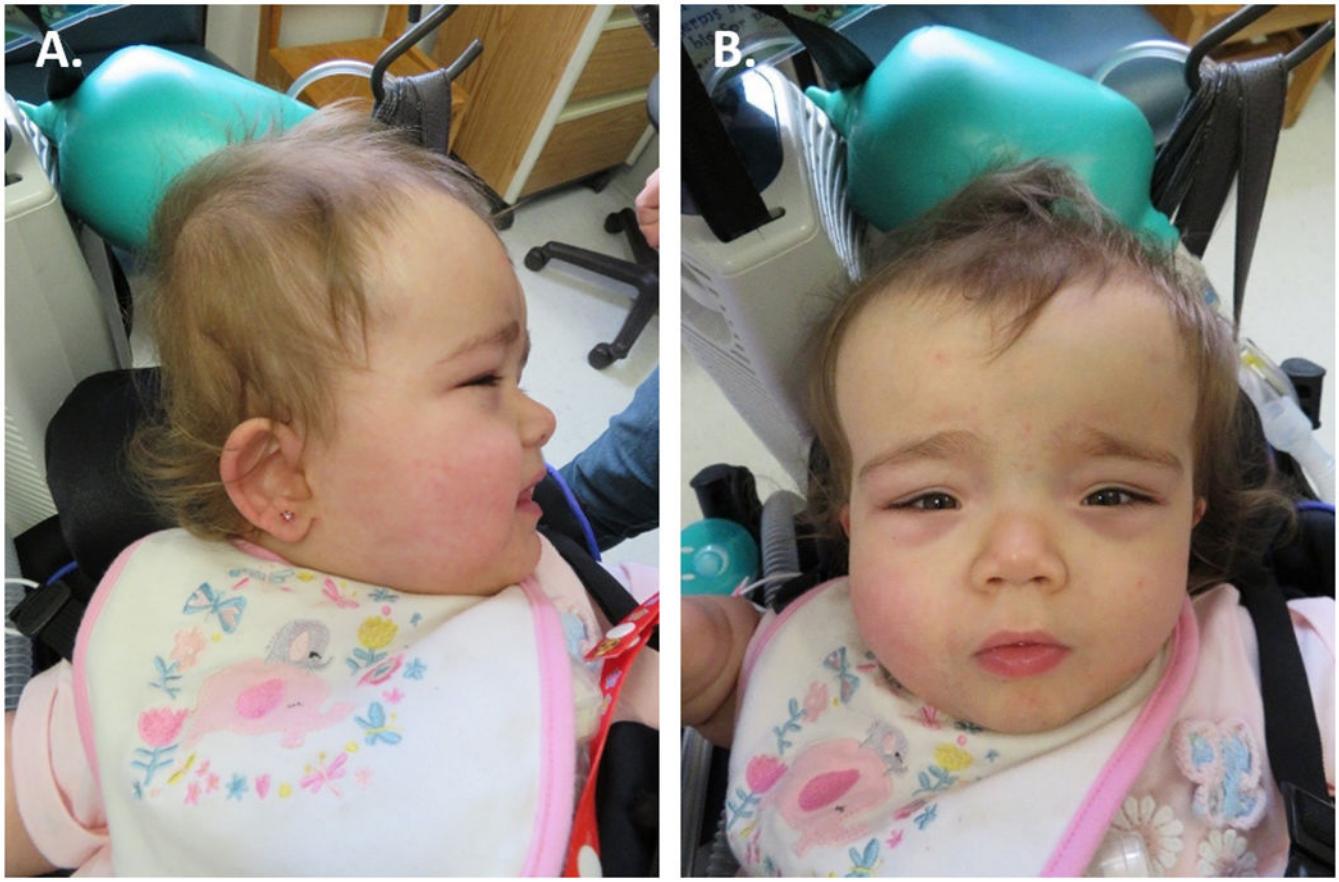

Figure 3:
The patient at age 20 months. A. Right lateral view. Note the brachycephaly, occipital flattening, depressed nasal bridge, and cupped and prominent ear. B: Frontal view. Note the macrocephaly, broad forehead, telecanthus, ocular hypertelorism, and depressed nasal bridge.

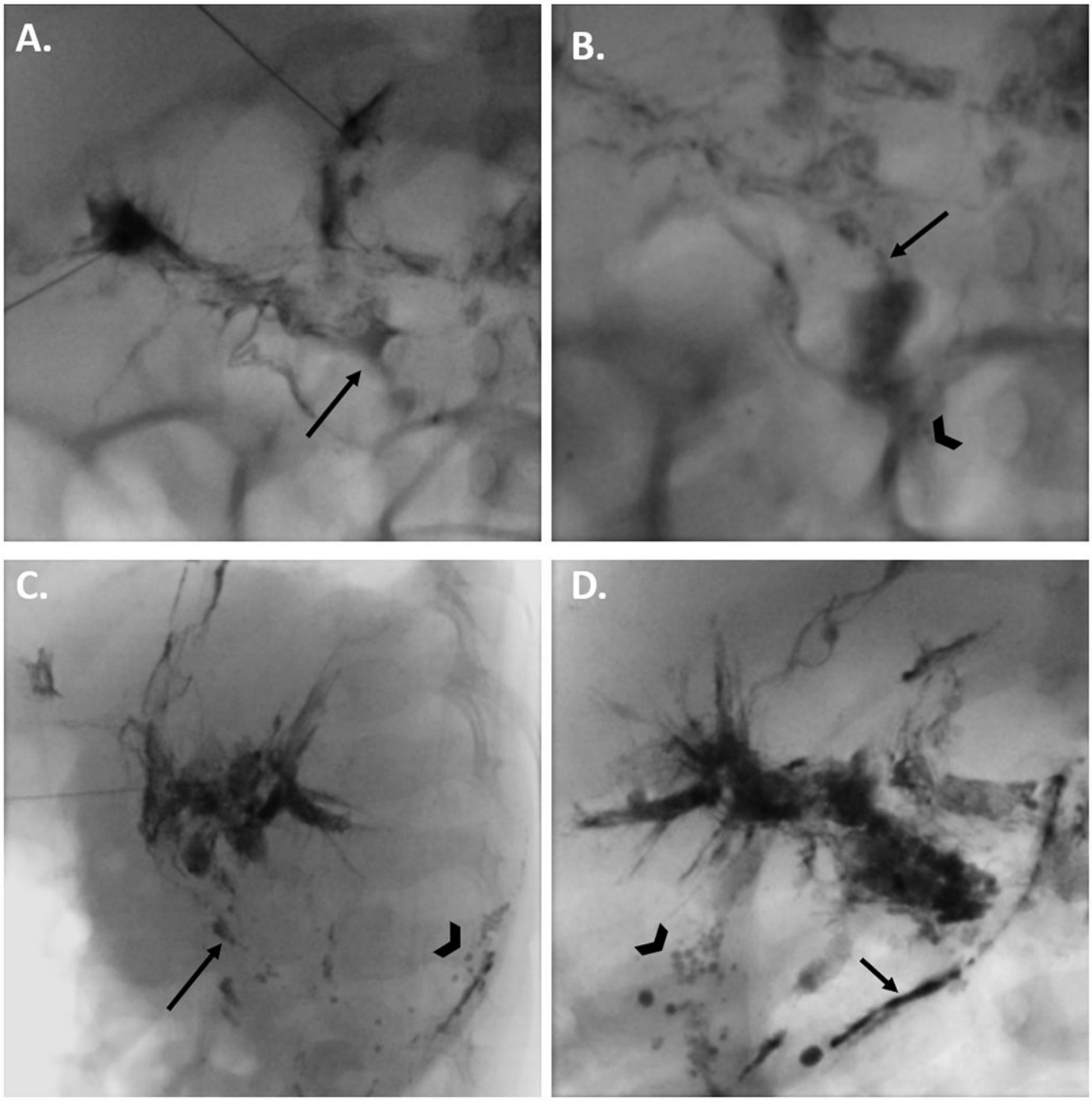

Figure 4:
The patient at 22 months. A. AP projection of dynamic contrast magnetic resonance lymphangiogram of the liver with Optiray 350 demonstrating extravasation of contrast material into the peritoneal space (arrow). B. AP projection of contrast liver lymphangiogram with Lipiodol showing leak of oil droplets out of the liver in the peritoneal space (arrow) with pooling of contrast medially (arrowhead). C. Lateral projection of contrast liver lymphangiogram with Lipiodol showing leak of oil droplets out of the liver in the peritoneal space (arrow) with pooling of contrast posteriorly (arrowhead). D. AP

projection of the liver after embolization of the liver lymphatic ducts with TrueFill glue demonstrating leak of glue from the liver along the liver capsule (arrow) and pooling in the peritoneum (arrowhead).