A 32-year-old pregnant woman was admitted to the hospital at 23.1 weeks of gestation, because of an abnormal fetal ultrasound study.

Approximately 15 weeks earlier, a home urine test for human chorionic gonadotropin confirmed an unplanned but highly desired pregnancy. A sonogram of the pelvis 14.5 weeks before admission revealed a single gestational sac containing an embryo that was consistent with a gestational age of 8 weeks 4 days; the uterus, sac, and embryo appeared normal.

The patient came to the outpatient obstetrics office of this hospital at 11.7 weeks of gestation for her first prenatal visit. She felt well. One year earlier, she had delivered a full-term healthy child at this hospital. Hypertension had developed during labor, for which labetalol had been administered transiently postpartum. Testing for the human immunodeficiency virus had been negative 18 months earlier. She was of western European ancestry, and her parents, siblings, and child were healthy. Medications included a multivitamin and folate supplement; she had previously taken oral contraceptives. She had no known drug allergies.

The vital signs and physical examination were normal for the stage of pregnancy. The hematocrit was 33.9% (reference range, 36.0 to 46.0) and the mean corpuscular volume 79 μm³ (reference range, 80 to 100); the remainder of the complete blood count was normal. The blood type was A, Rh-positive, and screening for irregular antibodies was negative. A test for rubella antibody was positive, and tests for syphilis and hepatitis B surface antibody were negative, as was a cervical swab for Chlamydia trachomatis and Neisseria gonorrhoeae. A Papanicolaou smear of the cervix displayed acute inflammation but was otherwise normal.

Approximately 7 weeks before admission, at 15.7 weeks of gestation, the blood pressure was 120/80 mm Hg. A second-trimester serum quadruple screening test (for alpha-fetoprotein, unconjugated estriol, human chorionic gonadotropin, and inhibin A) revealed a risk of Down's syndrome of 1 out of 1700 and a risk of trisomy 18 of 1 out of 13,000.

Nineteen days before admission, a sonogram revealed a single active fetus with a normal heart rate and amniotic-fluid volume. There was a prominent nuchal fold

From the Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT (C.J.L.); the Departments of Obstetrics and Gynecology (A.S.N.), Pediatrics (M.E.K.), and Pathology (D.J.R.), Massachusetts General Hospital, Boston; and the Departments of Obstetrics, Gynecology, and Reproductive Biology (A.S.N.), Medicine (M.E.K.), and Pathology (D.J.R.), Harvard Medical School, Boston.

that was at least 8 mm thick, bilateral nuchal cystic hygromas, a trace pericardial effusion, bilateral small pleural effusions, and mild bilateral pyelectasis. The inferior vena cava was large, and the fetal stomach was underfilled. The cæcum septum pellucidum was not identified, but part of the corpus callosum was seen. The placenta was low and posterior, reaching the cervix, and the cervix was longer than 3 cm and had no funneling. The remainder of the fetal cord and placental anatomy appeared normal.

The next day, ultrasonography confirmed the presence of nuchal edema and pleural effusions. The peak systolic velocity in the middle cerebral artery was normal. Amniocentesis was performed, which subsequently revealed a normal male karyotype. Testing of maternal serum for IgG and IgM antibodies to cytomegalovirus (CMV) and toxoplasma and for syphilis was negative. Testing for parvovirus IgG antibodies was positive, but it was negative for parvovirus IgM antibodies. An echocardiogram showed a left-sided fetal heart with normal segmental anatomy, chamber dimensions, and wall motion. There were bilateral fetal pleural effusions with no evidence of right ventricular dysfunction or elevated systemic venous pressures, and the ventricular outflow tract on the right was slightly smaller than that on the left. Six days later, magnetic resonance imaging (MRI) revealed normal fetal brain tissue, moderate bilateral pleural effusions, mild pyelectasis, and diffuse subcutaneous edema of the upper torso, upper thorax, and scalp. Five days before admission, ultrasonography of the uterus revealed an active fetus with a normal heart rate and amniotic fluid volume, persistent pleural effusions, and skin thickening primarily in the upper thorax and scalp.

After extensive discussion, the patient elected to proceed with termination of the pregnancy. The pregnancy was terminated by amnioinfusion with hypertonic saline and prostaglandins, and a stillborn 850-g male fetus was delivered vaginally. A fetal autopsy was performed.

**Differential Diagnosis**

*Dr. Charles J. Lockwood:* May we review the imaging studies?

*Dr. Allan S. Nadel:* An axial view of the fetal head at 20 weeks of gestation showed nuchal edema (Fig. 1A). Sonographic evaluation of nuchal edema—a finding associated with a variety of fetal abnormalities—was first described in the axial plane in the second trimester. Now we most often evaluate nuchal edema by measuring nuchal translucency in a midsagittal plane in the first
The thickness of the nuchal skin fold in this case is 8 mm; a thickness of more than 5 or 6 mm is considered abnormal at this point in gestation. Small bilateral cystic hygromas were also present. A longitudinal view of the fetus (Fig. 1B) shows pleural effusions but no ascites.

Anemia is an important cause of generalized fetal edema. In fetuses with anemia, the systolic velocity in the middle cerebral artery is increased, probably reflecting increased cardiac output and cerebral vasodilatation. In this case, the velocity was normal (Fig. 1C), indicating that this fetus was not anemic. Two weeks later, the pleural effusions were larger and the skin edema was worse, but there still was no ascites. The absence of ascites indicates that the edema is localized rather than generalized. It therefore suggests a local rather than a systemic cause.

**Dr. Lockwood:** May we see the echocardiogram?

**Dr. Mary Etta King:** The patient was referred at 20 weeks of gestation because of an abnormal fetal ultrasound examination that included pleural and pericardial effusions. Cardiac abnormalities can cause fetal edema and effusions. Assessment that is important in this context includes ventricular and valvular function, the diameters of the valves and outflow tracts, and the status of the foramen ovale. In this case, the ventricular function was normal and the diameters of the valve annuli were normal for the gestational age.

**Figure 2. Echocardiography of the Fetus at 20 Weeks of Gestation.**

An image of the fetal right ventricular outflow tract (Panel A) shows a measurement of the pulmonary annulus (P Ann). The annulus measured 3.9 mm in diameter (z = −0.2). The normal range for pulmonary annular dimension at 20 weeks is 2.8 to 5.2 mm, with a mean of about 4 mm. MPA denotes main pulmonary artery. Panel B shows a color-flow Doppler image within the right ventricular outflow tract and pulmonary artery, with the blue area indicating low-velocity anterograde flow. There was no evidence of outflow tract obstruction at any level. Panel C shows an image of the fetal aortic annulus (Ao Ann) and proximal ascending aorta (AscAo). The aortic annulus measured 4.1 mm in diameter (z = 1.5). The diameter of a normal aortic annulus for a fetus at 20 weeks of gestation measures between 2.6 and 4.2 mm, with a mean of 3.4 mm. The ascending aorta was dilated, and the diameter measured 5 mm (z = 3). The diameter of a normal ascending aorta for a fetus at 20 weeks of gestation is 2.5 to 4.4 mm, with a mean of 3.5 mm.
The four-chamber view shows a color Doppler image of flow across the tricuspid and mitral valves. There was no significant regurgitation across either atrioventricular valve, and Doppler inflow velocity patterns were normal, features that rule out valvular stenosis. The atria were normal in size.

There was no evidence of outflow obstruction either proximally or distally across the pulmonary outflow tract. The diameter of the pulmonary annulus was 3.9 mm (z = −0.2) (Fig. 2A), which is just slightly smaller than average for a fetus at 20 weeks of gestation. Images of the aortic root and arch showed no evidence of coarctation or outflow obstruction (Fig. 2B). The proximal ascending aorta was dilated, with a z value of 3. The diameter of the aortic annulus was normal for the gestational age, measuring 4.1 mm (z = 1.5) (Fig. 2C). Although the measurement of the right ventricular outflow tract was a little smaller than the aortic measurement, the difference was quite small and not significant.

Views of the interatrial septum showed the flap valve of the fossa ovalis moving from the right to the left, with evidence of shunt flow from the right atrium through the fossa into the left atrium, as one would expect in the fetus, and no obstruction was noted at the level of the fossa ovalis. The ductus arteriosus was patent, with unobstructed flow between the pulmonary artery and the descending aorta. The inferior vena cava was prominent, and there was evidence of bilateral pleural effusions (see video, available with the full text of this article at NEJM.org).

In summary, the fetus had a structurally normal heart, with normal rate and rhythm, normal ventricular function, no atrioventricular-valve regurgitation or stenosis, and no appreciable pericardial effusion. However, there were bilateral pleural effusions and mild dilatation of the ascending aorta.

Dr. Lockwood: These sonographic findings are consistent with fetal hydrops (also known as hydrops fetalis), which complicates 1 out of 3000 pregnancies. By convention, the diagnosis of hydrops fetalis requires the presence of fluid collections in two or more intraterine locations, including pleural effusion, ascites, pericardial effusions, subcutaneous edema, and polyhydramnios. This fetus displayed subcutaneous edema and bilateral pleural effusions. Fetal hydrops has two major causative categories: alloimmune hemolytic anemia and nonimmune hydrops fetalis. In this case, the absence of antibodies to red-cell antigens and the normal systolic velocities in the middle cerebral artery rule out alloimmune hemolytic anemia. Indeed, since the introduction of anti-D immune globulin therapy, more than 90% of the cases of hydrops fetalis have nonimmunologic causes.

Figure 3 outlines the potential pathogenic processes that lead to nonimmune hydrops fetalis. The differential diagnosis of the disorder is extensive. Table 1 lists general diagnostic categories and their relative contribution to nonimmune hydrops fetalis. The finding of normal velocities in the middle cerebral artery also rules out nonimmune causes of fetal anemia such as fetal-maternal hemorrhage, parvovirus B19 infection, pyruvate kinase deficiency, glucose-6-phosphate isomerase deficiency, glucose-6-phosphate dehydrogenase deficiency, Diamond–Blackfan anemia, and α-thalassemia. Twinning-related causes are also ruled out, since this is a singleton gestation.

GENETIC SYNDROMES ASSOCIATED WITH NUCHAL HYGROMBAS AND NONIMMUNE HYDRPES FETALIS

This fetus had small bilateral nuchal cystic hygromas. Discrete genetic syndromes characterized by both cystic hygromas and nonimmune hydrops fetalis should therefore be considered (see Table 1 of the Supplementary Appendix, available with the full text of this article at NEJM.org). Familial nuchal bleb, an autosomal recessive disorder, is accompanied by greatly elevated levels of amniotic fluid alpha-fetoprotein not seen in this case. Noonan’s syndrome, typically an autosomal dominant disorder most often caused by mutations involving the PTPN11 gene and less frequently the NF1 or KRAS genes, is characterized by nuchal hygromas and hydrops. In these cases, ultrasound findings include hypertelorism together with either pulmonic stenosis or hypertrophic cardiomyopathy, features not present in the sonograms of this fetus. Lethal multiple pterygium syndrome (autosomal recessive) has been linked to mutations in the CHRNG gene for the gamma subunit of the acetylcholine receptor; sonographic findings include multiple pterygia and akinesia, which were not present in this case. Camptomelic dysplasia (autosomal recessive) features generalized lymphedema, bowed and shortened long bones,
Elejalde syndrome (autosomal recessive) is characterized by polyhydramnios and omphalocele, which were also not observed in this case. 

Thoracoabdominal syndrome is an X-linked dominant disorder in which cleft palate, omphalocele, diaphragmatic hernia, and cardiac anomalies, such as transposition of the great vessels, accompany hygromas and hydrops. 

Again, none of these findings were present in this fetus. Lymphedema distichiasis syndrome (autosomal dominant), caused by a four-nucleotide (GGCC) duplication at position 1093 in the FOXC2 gene, is manifested as hand and foot lymphedema, arachnoid cysts, and cleft palate, all of which were absent in this case.

Figure 3. Pathogenesis of Nonimmune Hydrops Fetalis.
The primary pathogenic processes leading to nonimmune hydrops fetalis are increases in hydrostatic pressure, decreases in colloid oncotic pressure, and increases in blood and lymphatic vascular permeability. Multiple diseases can trigger any or all of these primary processes. For example, cardiac failure can lead to volume overload and increased hydrostatic pressure, whereas resultant tissue ischemia can directly increase vascular permeability or indirectly promote this phenomenon by increasing placental synthesis of soluble Fms-like tyrosine kinase-1 (sFlt). Increased vascular permeability can also result from elevated cytokine levels accompanying fetal infections or vascular involvement from lysosomal storage disease. Fetal anemia can lead to high-output cardiac failure or, in many cases, extramedullary hematopoiesis. Extramedullary hematopoiesis can cause the failure of hepatic protein synthesis, thus decreasing colloid oncotic pressure. Other causes of hepatic failure include infections, lysosomal storage disease, tumors, and lymphedema. Renal diseases, such as those caused by congenital nephrosis, lysosomal storage disease, and lymphedema, can decrease colloid oncotic pressure because of proteinuria. Lymphatic disorders contribute to hydrops directly by disruption of lymphatic vessels and secondarily by inducing chylothorax, which — if associated with mediastinal shifts — impairs venous return and induces cardiac tamponade, causing cardiac failure.
Hydrops in these cases can result from chylothorax, which reduces cardiac output by means of tamponade, decreased venous return, or both. Hydrops may also result from intrinsic cardiac defects or fetal akiinesia, which decreases lymphatic flow and increases intrathoracic pressure by means of diaphragmatic paralysis. In this case, the small size of the putative hygromas and the absence of other anomalies militate against these diagnoses.

The presence of normal fetal movements also rules out disorders of primary fetal akiinesia\textsuperscript{16-18} (see Table 2 in the Supplementary Appendix). Of these, Neu–Laxova syndrome (autosomal recessive) is also ruled out by the absence of the characteristic microcephaly, marked fetal growth restriction, brain malformations and severe propotis, hypertelorism, and micrognathia.\textsuperscript{16} Pena–Shokeir syndrome (autosomal recessive) and arthrogryposis multiplex congenita (autosomal recessive) would produce marked contractures.\textsuperscript{17} The most prominent features of congenital myotonic dystrophy type 1 (autosomal dominant), caused by expansion of a trinucleotide (CTG) repeat in the myotonin gene that frequently occurs in parent-to-child transmission, are marked polyhydramnios (100% of cases of this disorder), talipes (26.6%), and borderline ventriculomegaly (13.3%), all of which were absent in this case.\textsuperscript{18}

**CARDIAC CAUSES**

Hydrops can result from low-output cardiac failure due to intrinsic cardiac structural defects, vascular obstructions, and bradyarrhythmias or high-output cardiac failure due to tachyarrhythmias or extrinsic vascular tumors\textsuperscript{6} (see Tables 3 and 4 in the Supplementary Appendix). The most common structural defects associated with nonimmune hydrops fetalis are atrioventricular canal defects (20 to 29% of cases of cardiac anomaly–related nonimmune hydrops fetalis), left heart hypoplasia (24 to 27%), right heart hypoplasia (11 to 15%), and premature closure of the foramen ovale (6 to 15%) and the tetralogy of Fallot (4 to 6%). The most common tachyarrhythmia is supraventricular tachycardia, followed by atrial flutter, the Wolff–Parkinson–White syndrome, and rarely, severe forms of long-QT syndrome and other ventricular tachycardias. Half of bradyarrhythmias (complete heart block) result from an anatomical defect in the conduction system and half from

<table>
<thead>
<tr>
<th>Table 1. Primary Causes of Nonimmune Hydrops Fetalis (NIHF) and Their Relative Frequency.\textsuperscript{*}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Structural cardiac defects</td>
</tr>
<tr>
<td>Tachyarrhythmias</td>
</tr>
<tr>
<td>Bradyarrhythmias</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Obstruction</td>
</tr>
<tr>
<td>Aneurysms</td>
</tr>
<tr>
<td>Vascular tumors (e.g., large placental chorioangiomas)</td>
</tr>
<tr>
<td>Twin disorders</td>
</tr>
<tr>
<td>Twin-to-twin transfusion syndrome</td>
</tr>
<tr>
<td>Twin reversed-arterial-perfusion syndrome</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Chromosomal abnormalities</td>
</tr>
<tr>
<td>Associated with prominent cystic hygromas</td>
</tr>
<tr>
<td>Associated with profound fetal akiinesia</td>
</tr>
<tr>
<td>Anatomical abnormalities</td>
</tr>
<tr>
<td>Thoracic lesions</td>
</tr>
<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
</tr>
<tr>
<td>Lethal skeletal dysplasia</td>
</tr>
<tr>
<td>Urinary tract and renal abnormalities</td>
</tr>
<tr>
<td>Prune belly</td>
</tr>
<tr>
<td>Finnish nephrosis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Fetal hepatic tumors</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Volvulus</td>
</tr>
<tr>
<td>Meconium peritonitis causing severe ascites</td>
</tr>
<tr>
<td>Metabolic disorders (e.g., lysosomal storage diseases)</td>
</tr>
<tr>
<td>Anemias</td>
</tr>
<tr>
<td>Genetic disorders causing fetal anemia</td>
</tr>
<tr>
<td>(\alpha)-Thalassemia</td>
</tr>
<tr>
<td>Diamond–Blackfan anemia</td>
</tr>
<tr>
<td>Red-cell enzyme defects</td>
</tr>
<tr>
<td>Other hematologic abnormalities</td>
</tr>
<tr>
<td>Fetal-to-maternal hemorrhage</td>
</tr>
<tr>
<td>Intraventricular hemorrhage associated with alloimmune thrombocytopenia</td>
</tr>
<tr>
<td>Primary lymphatic disorders</td>
</tr>
<tr>
<td>Congenital pulmonary lymphangiectasis leading to chylothorax</td>
</tr>
<tr>
<td>Generalized (systemic) lymphangiectasis syndrome</td>
</tr>
</tbody>
</table>

\textsuperscript{*} Data are adapted from Warsof et al.,\textsuperscript{4} Abrams et al.,\textsuperscript{5} Machin,\textsuperscript{6} Stevenson et al.,\textsuperscript{7} and Wieacker et al.\textsuperscript{8}
secondary autoimmune-mediated destruction of this system. In this case, the essentially normal fetal cardiac anatomy, wall motion, and heart rate make an intrinsic cardiac cause unlikely.

High-output failure can result from vascular abnormalities, including large (>4 cm) placental chorioangiomas, sacrococcygeal teratomas, neuroblastomas, hemangiomas, and large aneurysms. Low-output failure can result from venous obstruction involving portal and femoral veins and the inferior vena cava.

This fetus and its placenta displayed no signs of vascular tumors. However, this fetus had a questionably dilated inferior vena cava with a relative reduction in right as compared with left ventricular outflow, which is opposite the normal fetal pattern, raising the possibility of a mild venous obstruction.

**CHROMOSOMAL ABNORMALITIES**

The most common chromosomal abnormality linked to nonimmune hydrops fetalis is monosomy X (accounting for 42 to 67% of aneuploid cases). Hydrops follows lymphatic dysplasia, causing chylothorax or severe postductal coarctation. Another aneuploidy associated with nonimmune hydrops fetalis is trisomy 21 (23 to 34%). Potential pathogenic mechanisms for hydrops induced by Down’s syndrome include chylothorax, intrinsic cardiac disease (particularly atrioventricular canal defects), and congenital leukemia. Other chromosomal abnormalities that account for less than 10% of cases include trisomies 13, 16, and 18; triploidy; tetraploidy; 13q−, 17q−, and 18q+; and duplicated 11p. However, this fetus had a normal karyotype.

**INFECTIOUS CAUSES**

There are multiple infectious causes of nonimmune hydrops fetalis (see Table 5 in the Supplementary Appendix). Of these, parvovirus B19 appears to be the most common cause, followed by CMV. Bacterial causes include syphilis and *Listeria monocytogenes*; parasitic causes include *Toxoplasma gondii* and *Trypanosoma cruzi*. These infections induce hydrops through myocarditis, hepatic dysfunction with hypalbuminemia, increased vascular permeability, and rarely, leukemoid reactions. Parvovirus B19 induces bone marrow suppression with anemia-induced high-output cardiac failure and, rarely, cardiomyopathy. In this case, there were no sonographic signs of congenital infection (e.g., cerebral ventriculomegaly and cerebral or hepatic calcifications), and the velocities in the middle cerebral artery were normal. Moreover, serologic analysis of the mother for rubella, CMV, toxoplasma, syphilis, and parvovirus showed no evidence of acute infection.

**ANATOMICAL ABNORMALITIES**

Chylothorax accounts for half the thoracic lesions associated with nonimmune hydrops fetalis. Other thoracic lesions include congenital cystic adenomatoïd malformation (18 to 28% of thoracic cases), diaphragmatic hernia (7 to 15%), pulmonary sequestration (8 to 9%), bronchiogenic cyst (1 to 4%), and rarely, the constrictive thoracic skeletal dysplasias, including short rib–polydactyly syndromes, lethal chondrodysplasia, thanatophoric dysplasia, and homozygous achondroplasia. Mechanisms of hydrops include impaired venous return to the heart and cardiac tamponade due to mass effects or high-output failure (caused by highly vascular tumors). In this case, repeated sonograms showed no such masses, skeletal dysplasia, or diaphragmatic hernia.

Urinary tract and gastrointestinal anomalies are rare causes of nonimmune hydrops fetalis. Congenital nephrosis leads to hydrops by inducing hypoproteinemia. However, this condition is associated with elevations in the levels of alphafetoprotein in maternal serum and amniotic fluid, which were not present in this case. The prune belly syndrome, due to posterior urethral valve or urethral atresia, probably causes hydrops by obstructing venous return or mechanical tamponade. Hepatic tumors, volvulus, and meconium peritonitis promote hydrops through hypoproteinemia, and isolated defects of the abdominal wall cause lymphatic obstruction. However, none of these anomalies were observed in this case.

**LYSOSOMAL STORAGE DISEASES**

Lysosomal storage diseases account for between 1 and 15% of the cases of nonimmune hydrops fetalis. Although at least 50 distinct lysosomal storage diseases have been reported, only a subgroup commonly triggers hydrops (see Table 6 in the Supplementary Appendix). An enzyme defect causes accumulation of substrate or metabolic products in lysosomes that ultimately leads to cell swelling, dysfunction, and death in the liver, brain,
heart, and kidneys. Hydrops results from an increase in hydrostatic pressure due to obstruction of venous return by visceromegaly or cardiomyopathy, a decrease in oncotic pressure due to hepatic or renal dysfunction, an increase in lymphatic or blood-vessel permeability, and late-onset anemia. In this case, the potentially dilated inferior vena cava and relatively reduced size of the right heart could reflect a mass effect from hepatomegaly. However, findings incompatible with this diagnosis include the lack of ascites and restriction of edema to the upper body.

**LYMPHATIC DISORDERS**

Lymphatic disorders can lead to nonimmune hydrops fetalis. Primary congenital pulmonary lymphangiectasis reflects an abnormality of lymphatic development. Secondary forms of this disease can arise from thoracic-duct obstruction, thoracic masses, total anomalous pulmonary venous return, or as a component of the discrete syndromes discussed previously (see Table 1 in the Supplementary Appendix). The resultant chylothorax leads to hydrops by reducing venous return or inducing cardiac tamponade. Case reports suggest that pleuroamniotic shunting at midgestation may prevent pulmonary hypoplasia and, when coupled with aggressive neonatal intervention, could improve on an otherwise lethal prognosis. Generalized lymphangiectasis results from systemic ectasia of the lymphatic vessels. In this condition, subcutaneous edema and hepatic, pancreatic, and renal lymphedema occur concomitantly with chylothorax. Hydrops results from gastrointestinal protein loss, renal involvement, decreased cardiac output, and diffuse lymphatic leak. The pulmonary and generalized variants may reflect variable manifestations of the same disorder and can occur sporadically or by autosomal recessive inheritance.

The findings in this case do not readily lend themselves to a single diagnosis. The apparent dilatation of the inferior vena cava could reflect hepatomegaly due to a lysosomal storage disease; however, the predominance of edema in the upper body and the lack of ascites strongly militate against this diagnosis. Noonan's syndrome is unlikely in the absence of cardiac defects. The lymphangiectasis syndromes could produce the upper-body edema that was observed in association with the bilateral chylothorax. Moreover, the mildly dilated inferior vena cava could result from lymphatic induced hepatic or pancreatic edema. Thus, lymphangiectasis syndrome is the most likely diagnosis, particularly congenital pulmonary lymphangiectasis (see Fig. 1 in the Supplementary Appendix).

**Dr. Nancy Lee Harris (Pathology):** Dr. Tracy, would you tell us what happened next?

**Dr. Erin E. Tracy (Obstetrics and Gynecology):** The patient was counseled extensively regarding the differential diagnosis and the very poor prognosis, given the worsening scalp edema and pleural effusions during such a short interval. A number of potential diagnoses had been effectively ruled out or determined to be very unlikely, since the workup had included a normal amniocentesis, normal fetal cardiac echocardiogram, normal MRI, normal infectious disease workup (indicating either previous immunity or lack of exposure to a number of agents), and a normal Doppler study of the middle cerebral artery (making fetal anemia an unlikely cause). The lack of generalized ascites was also noteworthy.

After much counseling and deliberation, she elected to have a pregnancy termination. We had encouraged her to have a saline infusion to help our pathologists identify the potential underlying cause for the fetal ultrasound findings. Supportive services were offered as well.

**Clinical Diagnosis**

Nonimmune hydrops fetalis.

**Dr. Charles J. Lockwood’s Diagnosis**

Lymphangiectasis syndrome, probably congenital pulmonary lymphangiectasis.
nation showed marked villous edema, confirming the diagnosis of hydrops placentalis.

The male fetus had marked edema limited to the head and neck. Body weight and measurements were as expected for 22 weeks of gestational. There were no prominent dysmorphic features, although the eyes were mildly hyperteloristic. The internal examination showed marked bilateral cloudy pleural effusions, 20 ml in total. The lungs were hypoplastic, weighing 6 g combined (12 g would be expected for 22 weeks of gestation). There was no pericardial effusion or ascites. There were no gross structural anomalies. The heart was structurally normal, appropriate for gestational age.

Histologic examination of the organs showed normal development without abnormal histopathological findings in all organs except the lungs. In the lungs, there was marked lymphangiectasia, which was prominent in the perihilar tissues (Fig. 4A) and subpleural regions (Fig. 4B) but also was present in the interstitium. Examination of tissues from the neck and scalp revealed only dermal edema and mild lymphangiectasia. Our protocol for cases of nonimmune hydrops includes sending fetal and placental tissues for karyotyping and for microbiologic and viral cultures. We also examine a blood spot from the fetus to test for the common inborn errors of metabolism. We save fresh and frozen liver, skin, and bile for biochemical studies, if needed. A peripheral-blood smear is made if possible. Radiographs are obtained for analysis of the skeletal development. The results of all these tests were normal.

The histopathological findings are diagnostic of congenital lymphangiectasia restricted to the lungs. The finding of placental hydrops may occur in both pulmonary and generalized lymphangiectasia. We were left with two possible diagnoses: congenital pulmonary lymphangiectasia or Noonan’s syndrome. Noonan’s syndrome is a common autosomal dominant genetic disorder diagnosed at birth with a constellation of variable dysorphic facies and bony abnormalities of the chest, as well as the cardiac abnormalities described by Dr. Lockwood. Pulmonary lymphangiectasis may be present and is due to malformations of the pulmonic valve, typically pulmonic stenosis. Since the sternum was normal (not shieldlike), there was no kyphoscoliosis, the only dysmorphic finding was the mild hypertelorism, and the cardiac morphology was appropriate for gestational age, we preferred the diagnosis of congenital pulmonary lymphangiectasia, although we could not completely rule out the possibility of Noonan’s syndrome.

The cause of congenital pulmonary lymphangiectasia is unknown but is thought to be due to obstruction of the lymphatic duct. A study reported increased endothelial nitric oxide synthetase in the pulmonary arteries and lymphatics in autopsy tissue from a fetus with congenital pulmonary lymphangiectasia, as compared with the amount in tissue from infants with normal lungs. The diagnosis is typically made after delivery, when patients present with respiratory compromise that often does not respond to treatment and is associated with a high mortality rate. Pathological findings in reported cases

**Figure 4.** Histologic Images of Fetal Lung Specimens (Hematoxylin and Eosin).
Panel A shows perihilar lymphangiectasia, and Panel B shows subpleural lymphangiectasia. The arrows point to dilated lymphatics.
are similar to those in this case, with dilated lymphatics in the lungs and normal lymphatics elsewhere.\textsuperscript{27} The placenta has not been well studied in the reported cases. Hydrops fetalis is common in Noonan’s syndrome and is thought to be a complication of the cardiac pathological changes.

\textbf{Dr. Harris:} Dr. Tracy, how did you counsel this patient, and has she had subsequent pregnancies?

\textbf{Dr. Tracy:} Because of the reported familial occurrence of congenital lymphangiectasis, we referred the patient to Dr. Lewis Holmes of Medical Genetics for genetic counseling. Since there is no genetic testing for the familial form of the disease, no specific estimate of risk could be given, except that reported cases appear to be mainly autosomal recessive, so the chance of a second affected fetus would be 25\% or less. The patient became pregnant again and delivered a healthy infant 1 year after the termination of this pregnancy.

\section*{Anatomical Diagnosis}

Hydrops fetalis and hydrops placentalis due to fetal (congenital) pulmonary lymphangiectasia.

Dr. Lockwood reports receiving income for his roles as editor in chief of \textit{Contemporary OB/GYN} and as editor of the obstetrics section of \textit{UpToDate}. No other potential conflict of interest relevant to this article was reported.

We thank Dr. Bryann Bromley of the Obstetrics and Gynecology Service at Massachusetts General Hospital for performing the 20-week ultrasound examination and Dr. Judy Becker, director of the fetal cardiac ultrasound program at Massachusetts General Hospital, for performing the fetal echocardiography.

\section*{REFERENCES}


28. Moerman P, Vandenbergh K, Dev-

\newpage

\section*{ANATOMICAL DIAGNOSIS}

Hydrops fetalis and hydrops placentalis due to fetal (congenital) pulmonary lymphangiectasia.
lieger H, Van Hole C, Fryns JP, Lauweryns JM. Congenital pulmonary lymphangiec-
tasis with chylothorax: a heterogeneous lymphatic vessel abnormality. Am J Med
Genet 1993;47:54-8.
tasis sequence: a rare, heterogeneous, and
lethal etiology for prenatal pleural effu-
R.M. Endothelial, inducible and neuronal
nitric oxide synthase in congenital pulmo-
nary lymphangiectasis. Eur Respir J 2006;
27:1311-5.
Pulmonary lymphangiectasia. Lymphol-
32. Xiao ZY, Tao Y, Tang XY, Chen GJ, Guo
L. Congenital pulmonary lymphangiecta-
Copyright © 2009 Massachusetts Medical Society.

LANTERN SLIDES UPDATED: COMPLETE POWERPOINT SLIDE SETS FROM THE CLINICOPATHOLOGICAL CONFERENCES

Any reader of the Journal who uses the Case Records of the Massachusetts General Hospital as a teaching exercise or reference material is now eligible to receive a complete set of PowerPoint slides, including digital images, with identifying legends, shown at the live Clinicopathological Conference (CPC) that is the basis of the Case Record. This slide set contains all of the images from the CPC, not only those published in the Journal. Radiographic, neurologic, and cardiac studies, gross specimens, and photomicrographs, as well as unpublished text slides, tables, and diagrams, are included. Every year 40 sets are produced, averaging 50-60 slides per set. Each set is supplied on a compact disc and is mailed to coincide with the publication of the Case Record.

The cost of an annual subscription is $600, or individual sets may be purchased for $50 each. Application forms for the current subscription year, which began in January, may be obtained from the Lantern Slides Service, Department of Pathology, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-2974) or e-mail Pathphotoslides@partners.org.