TABLE 1.—*Erythropoietin Assay Results*

Materials Assayed	*% RBC-^{59} Fe Uptake**	*Equivalent U/liter*
Saline	0.31 ± 0.04	ND
Erythropoietin		
50 U	2.12 ± 0.40	50
200 U	6.89 ± 0.76	200
800 U	13.93 ± 1.65	800
Normal human serum, female	0.55 ± 0.12	ND
Patient's serum, before	9.43 ± 1.10	420
Patient's serum, before, plus antierythropoietin	0.61 ± 0.31	ND
Patient's serum, after	0.87 ± 0.21	ND
Tissue extract	5.77 ± 0.87	150
Tissue extract plus antierythropoietin	0.33 ± 0.05	ND

ND=not detectable, RBC-^{59}Fe=erythrocytes labeled with radioactive iron

*The results from 5 mice per group are given as the mean plus 1 standard error of the mean.

Discussion

When the patient presented with a high hematocrit and a locally advanced breast cancer, ectopic erythropoietin hormone production was a theoretically possible cause. Leukocyte and platelet counts were normal, the erythrocyte volume was increased, an intravenous pyelogram revealed no renal mass, and a liver-spleen scan was normal. A breast biopsy was needed for estrogen- and progesterone-receptor determinations, and arrangements were made to study erythropoietin values on specimens of blood and biopsy tissue. Both were elevated. She also had hypertension, and catecholamine values were elevated; these findings persisted after irradiation and mastectomy, even though the hematocrit had fallen to 0.40. There is no likely connection between the presence of the two humoral abnormalities.

Neoplasms associated with the ectopic production of erythropoietin include renal cell carcinoma, cerebellar hemangioblastoma, hepatic angiosarcoma, hepatoma, pheochromocytoma, large renal cysts, uterine fibromyoma, and tumors of the thymus, lung, adrenals and ovaries.[3-10] As in the present study, the increased production of erythropoietin in most of these cases was documented using the polycythemic mouse assay, which provides a quantitative evaluation of biologically active erythropoietin from human and animal sources.[5-9] Although the polycythemic mouse assay is relatively insensitive and cannot reliably detect erythropoietin levels below 50 U per liter, erythropoietin levels in patients with tumor-associated erythrocytosis have been generally high—420 U per liter in this patient—and easily detectable. The radioimmunoassay for erythropoietin,[11] now available from commercial sources, is a more sensitive assay procedure and can be used to assess physiologically significant changes in erythropoietin production in clinical disorders of erythropoiesis. We have not been able to find any previous reports in the literature of a primary breast cancer associated with erythrocytosis. Although some fall in the hemoglobin and hematocrit levels due to radiotherapy of the chest wall would be expected, this should in fact result in an increase of the level of erythropoietin and not a diminution as occurred in this patient. Therefore, a fall in both the hematocrit and erythropoietin to normal levels after eradication of the tumor by irradiation and surgical therapy strongly suggests that the breast cancer in this patient was the source of the excessive erythropoietin production. This is further reinforced by the presence of large amounts of erythropoietin in the neoplastic tissue as found by our assays.

Adenocarcinoma of the breast should be added to the list of neoplasms to be considered in the differential diagnosis of unexplained or "inappropriate" erythrocytosis.

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Prenatal Diagnosis of Noonan's Syndrome in a Female Infant With Spontaneous Resolution of Cystic Hygroma and Hydrops

LUIS IZQUIERDO, MD
ORI KUSHNIR, MD
DIANE SANCHEZ, MD
LUIS CURET, MD
PATRICIA OLNEY, MS
GLORIA E. SARTO, MD, PhD
CAROL CLERICUZIO, MD
Albuquerque

RICHARD OLNEY, MD
Gallup, New Mexico

THE NOONAN SYNDROME is one of multiple congenital anomalies that may occur on a sporadic basis or in a pattern consistent with an autosomal dominant inheritance.[1,2] The pathogenesis remains unknown and the expression is variable.[1,2] It has been associated with a spectrum of congenital abnormalities. Some of the phenotypic malformations include ptosis, pterygium colli, cryptorchidism, short stature, heart defect, and the jugular obstructive lymphatic sequence.[1,2]

Cystic hygromas are congenital malformations of the

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From the Departments of Obstetrics and Gynecology (Dr Izquierdo, Dr Kushnir, Dr Sanchez, Dr Curet, Ms Olney, and Dr Sarto) and Pediatrics (Dr Clericuzio), University of New Mexico Hospital, Albuquerque, and the Department of Pediatrics, Gallup Indian Medical Center, Gallup, New Mexico (Dr Olney).

Reprint requests to Luis Izquierdo, MD, Department of Obstetrics and Gynecology, University of New Mexico School of Medicine, 2211 Lomas Blvd NE, Albuquerque, NM 87131.

lymphatic system that appear as fluid-filled cavities most commonly found in the posterior cervical area.[3,4] Posterior cervical hygroma is a rather nonspecific malformation found in a number of unrelated conditions that reflects a failure or delay in the development of the connection between the jugular lymph sac and the internal jugular vein.[4] Frequently cystic hygromas are found in association with chromosomal aberrations.[3,5] When cytogenetic studies are normal, Noonan's syndrome should be included in the differential diagnosis.[4,6-8] We report a case of Noonan's syndrome in a female fetus accompanied by the spontaneous resolution of a fetal cystic hygroma and hydrops, and followed by the delivery of a term live-born infant.

Report of a Case

The patient, a 19-year-old gravida 1, para 0 woman at 29 weeks' gestation, was referred to the High Risk Obstetrical Unit at the University of New Mexico, Albuquerque, for preterm labor. An ultrasonogram done on admission revealed a single living fetus with a biparietal diameter of 73 mm, an abdominal circumference of 255 mm, and a femur length of 56 mm, all consistent with an estimated fetal age of 28 to 29 weeks. Also noted on this ultrasound examination was a large, cystic, septated nuchal mass (Figure 1), accompanied by generalized fetal edema, including scalp edema, pericardial effusion, and ascites (Figure 2). A diagnosis of cystic hygroma with hydrops was made. The patient was Rh-positive and had a negative indirect Coombs test. Fetal echocardiography was normal. The medical and family histories were unremarkable. A genetic history and the family pedigree were obtained, showing no evidence of previous anomalies in the family.

The patient received tocolytic therapy with terbutaline sulfate. After contractions subsided, an ultrasonogram was again done. No other structural anomalies were observed. The family was informed about the risks of chromosomal abnormalities. An amniocentesis for culture of amniotic fluid cells was done, a 46,XX karyotype determined, and 15 metaphases of 46 chromosomes were counted, with 5 being completely analyzed.

The patient was discharged home and was thereafter observed at her primary care facility. She returned to our clinic at 36 weeks and 6 days of gestation. On ultrasonogram the cystic hygroma had spontaneously disappeared, leaving only redundant skin and edema in the posterior cervical area. The hydrops had also resolved.

At 39 weeks, the patient went into active labor and was delivered of a single, living female child vaginally; Apgar

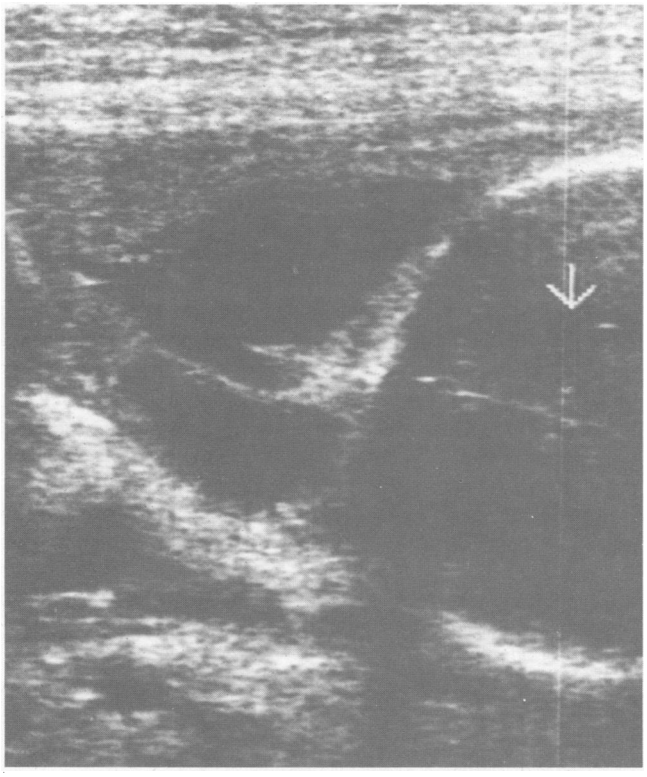

Figure 1.—An ultrasonogram view of the posterior craniocervical area of the fetus shows a large, cystic, septated mass.

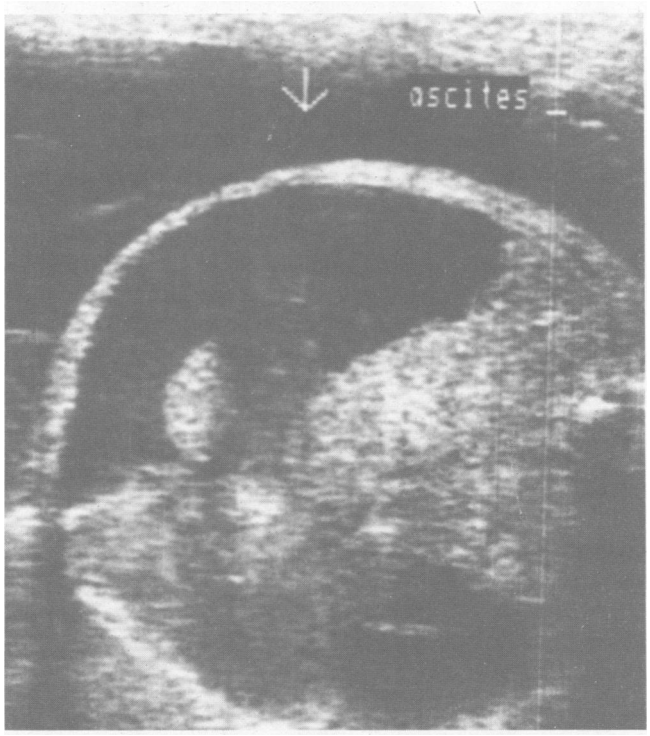

Figure 2.—A transverse section of the abdomen of the fetus shows ascites.

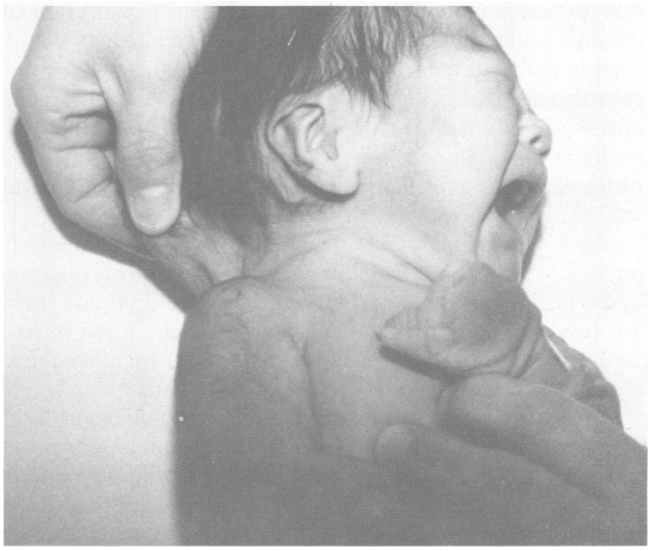

Figure 3.—The neonate after delivery shows evidence of pterygium colli and a low hairline.

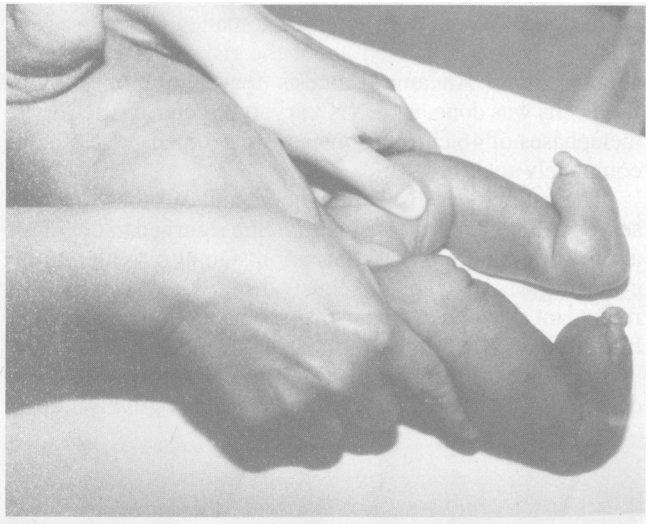

Figure 4.—Generalized lymphedema of feet and laxity of the abdominal wall are seen.

scores were 8 and 9 at one and five minutes, respectively. The infant weighed 3,140 grams (50th percentile).

Examination of the newborn by pediatricians and dysmorphologists showed the following: pterygium colli, generalized lymphedema of the hands, feet, and genitals (Figures 3 and 4), a low posterior hairline, and widely spaced nipples. A heart murmur was heard over the pulmonary valve area during systole, highly suggestive of pulmonary stenosis, and echocardiography was done. All these findings were consistent with Noonan's syndrome.

Cytogenetic studies of the infant's blood confirmed the 46,XX karyotype, with 20 metaphases of 46 chromosomes being counted and 10 analyzed completely.

Discussion

In the fetus, the lymphatic system drains into the jugular lymphatic sac. If the connection between the jugular vein and the lymphatic system does not occur (around 40 days of gestation), progressive peripheral lymphedema, hydrops, and cystic hygroma will develop.[3,5,9] This phenotype is recognized as the jugular lymphatic obstructive sequence.[10(pp472-473)] If the connection is subsequently formed, this sequence is interrupted, with resultant reabsorption of the fluid collections. A residual effect is a webbed neck (pterygium colli) due to redundant skin. Other consequences of overdistention of the jugular lymphatic sac are uplifting and anterior rotation of the ears with abnormal hair patterns. The peripheral lymphedema gives rise to redundancy of the skin of the face and puffy hands and feet.[5] Laxity of the ventral wall as a result of ascites has also been reported.[10(pp472-473)]

Cystic hygromas can be diagnosed by ultrasonography.[3-8,11-14] Characteristically, they present as posterolateral cystic masses having a midline septum. The skull and spine are intact and there are no solid components in the mass.[3] The differential diagnosis includes cervical meningoceles, encephaloceles, neck tumors, and nuchal edema.[5]

Previous studies have shown that the prenatal diagnosis of cystic hygroma and hydrops is associated with a poor prognosis irrespective of karyotype.[3,5] Romero and co-workers reviewed 40 cases reported in the literature, most of them involving hydrops, and 33% of infants died in utero, usually within a few weeks of the diagnosis, 5% died in the early neonatal period, and the rest were electively aborted. Still further evidence of a poor prognosis irrespective of karyotype in cases of cystic hygroma and hydrops was presented in 1989 by Abramowicz and colleagues at the Society of Perinatal Obstetricians in which only one of six fetuses with a normal karyotype survived.[15] Prognostic data on fetal cystic hygromas without associated hydrops are scanty.[5]

In Noonan's syndrome, the features of nuchal cystic masses and nonimmune hydrops have been identified by ultrasonography.[2,6-8,14] Additional information rendered by fetal echocardiography is a possible diagnosis of pulmonary valve stenosis.[1,2] Review of the literature reflects variable findings on amniotic fluid α-fetoprotein levels in the presence of cystic hygroma; some investigators report elevated levels whereas others report normal levels.[2,12]

In cases in which chromosome abnormalities, including monosomy or trisomy, are associated with cystic hygroma and hydrops, the recurrence risk will be low; chorionic villus sampling or amniocentesis, however, should be offered in subsequent pregnancies.[12] When chromosomal studies are normal, as in the Noonan syndrome, an autosomal dominant inheritance with a variable penetrance trait should be considered. In cases of Noonan's syndrome, monitoring of future pregnancies with ultrasonography and possibly fetal karyotyping should be suggested to provide reassurance to the family.[3]

Determination of the fetal karyotype should be recommended in all cases of cystic hygroma and hydrops. If the karyotype is normal, appropriate immunologic and viral studies are required and may be useful for counseling in the future.[5] Pregnancy interruption should be offered before viability,[5] although in patients with a normal karyotype the progression of the hygroma should be followed by ultrasonogram as the outcome may be normal.[8] After viability is reached, because of the dire prognosis, fetuses with hydrops should probably be managed nonaggressively.[5] A thorough search for associated anomalies must be done after delivery to corroborate the prenatal diagnostic findings.[13]

This case report supports the importance of including the Noonan syndrome in the differential diagnosis of fetal cystic hygroma and hydrops. It describes a fetus with spontaneous resolution of the jugular lymphatic obstructive sequence, who reached viability and was delivered at term, contrary to and different from most published reports.

This supports the consideration that fetuses with normal chromosomal studies and normal echocardiography, in the presence of cystic hygroma and hydrops, could be managed expectantly if the family desired to continue with the pregnancy.[8,14]

Furthermore, based on our personal observations and those of others, decompression of cystic hygromas guided by ultrasonography should be considered as an option for further investigation of these fetuses. Successful fetal karyotyping in cases of fetal cystic hygroma and oligohydramnios can be done from the hygroma fluid using standard culture techniques.[16]

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Chylothorax and Respiratory Failure in Kaposi's Sarcoma

DANIEL W. PENNINGTON, MD
MARTHA L. WARNOCK, MD
MICHAEL S. STULBARG, MD
San Francisco

DISSEMINATED KAPOSI'S SARCOMA (KS) is a common problem in patients with the acquired immunodeficiency syndrome, particularly in homosexual men. Intrathoracic involvement occurs clinically in as many as a fifth of patients with KS[1,2] and has been reported in 11 of 23 consecutive patients in an autopsy series.[3] Pulmonary KS usually, though not always, follows the appearance of characteristic lesions on the skin. Its clinical and radiographic presentation may mimic pneumonia due to opportunistic infections, although nodular infiltrates and intrathoracic lymph node enlargement are commonly seen. Pleural effusions occur in as many as half of patients with pulmonary KS; they may be bilateral and are often hemorrhagic. Although they result from tumor implants on the visceral pleura, neither cytologic examination of the fluid nor pleural biopsies are helpful in establishing the diagnosis.[3-5] Because pleural effusions only rarely occur in patients with *Pneumocystis carinii* pneumonia or other opportunistic infections, the presence of a pleural effusion in a patient with cutaneous KS suggests the diagnosis of pulmonary KS.[4] Among patients with pulmonary KS, those with pleural effusions have substantially shortened survival.[6] Chylous pleural effusions, on the other hand, have been reported previously in only two patients with KS.[7,8]

(Pennington DW, Warnock ML, Stulbarg MS: Chylothorax and respiratory failure in Kaposi's sarcoma. West J Med 1990 Apr; 152:421-422)

From the Departments of Medicine (Drs Pennington and Stulbarg) and Pathology (Dr Warnock), Cardiovascular Research Institute (Dr Pennington), University of California, San Francisco, School of Medicine.

Reprint requests to Daniel W. Pennington, MD, Box 0130, Cardiovascular Research Institute, UCSF, Third and Parnassus, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT
CT = computed tomographic
KS = Kaposi's sarcoma

Report of a Case

The patient, a 35-year-old homosexual man, had violaceous skin lesions develop in early 1986, and a skin biopsy in June of that year disclosed Kaposi's sarcoma. Although he had no pulmonary symptoms, a diffuse, interstitial pulmonary infiltrate was noted, and an opportunistic infection was suspected. Over the next six months, bronchoalveolar lavage was done on three occasions, but no diagnosis was established.

In February 1987, the patient was admitted to the hospital with chills and sweats. On examination he had many cutaneous KS lesions and enlarged left axillary and right submandibular lymph nodes. A chest radiograph revealed a diffuse pulmonary interstitial infiltrate and blunting of the right costophrenic angle, suggesting a small pleural effusion. The patient refused a diagnostic evaluation and was discharged against medical advice.

The patient was admitted again in April 1987 because of

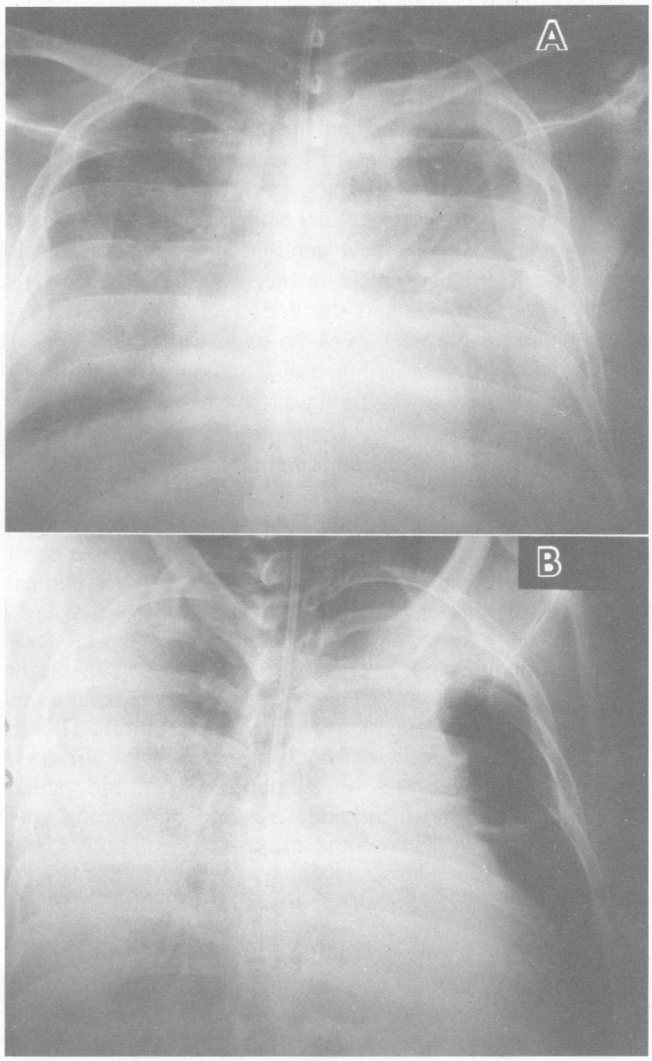

Figure 1.—A, Anteroposterior and, **B,** right-side-down decubitus chest films show bilateral large pleural effusions.