Three fetuses karyotyped as Turner syndrome with cystic hygroma developing hydrops: prognosis and outcome

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Summary

Introduction: We present three cases of fetuses diagnosed as Turner syndrome with cystic hygroma (CH) developing hydrops to discuss the prenatal diagnostic and prognostic criteria of CH in ultrasound and outcome of the fetuses.

Cases: The first case was 30-year-old pregnant woman with a nuchal translucency measurement of 8 mm at 12 weeks' gestation. Serial ultrasound examinations revealed non-septated cystic hygroma and hydrops. The pregnancy was terminated at the 18th week of gestation. Diagnosis of CH was made at 14 and 15 weeks of gestation in case 2 and case 3, respectively. Ultrasound revealed large cystic septated sacs in the nuchal area combined with serosal fluid collection and cutaneous edema. Spontaneous fetal demise occured at 21 and 16 weeks of gestation in cases 2 and 3, respectively. All fetuses were diagnosed as Turner syndrome.

Key words: Cystic hygroma; Turner syndrome; Hydrops fetalis; Outcome.

Introduction

Cystic hygroma (CH) is a well known lymphatic malformation occurring most commonly in the cervical region. It is believed to be a result of failure of communication between the lymphatic sacs and venous system [1]. Associated chromosomal abnormalities and a variety of other congenital malformations occur in the vast majority of cases [2]. The disease course of a fetus with CH is unpredictable. There is no reliable method for predicting which hygromas will regress and which hygromas are associated with aneuploidy and other anomalies. Progressive hydrops fetalis develops in up to 75% of cases and usually results in fetal demise in the ensuing weeks [3]. In this report, we describe three fetuses with CH karyotyped as Turner syndrome that developed hydrops fetalis. The prenatal diagnostic and prognostic criteria of cystic hygroma at ultrasound and outcome of these fetuses with cystic hygroma are discussed.

Case Reports

Case 1

A 30-year-old woman, gravida 3, para 2, was referred at 12 weeks of gestation for the first trimester screening test. Her past medical history was unremarkable and maternal serology was negative. There were no family history of congenital anomalies. Sonographic examination revealed a single viable fetus with a crown-rump length in agreement with her last menstrual period. Nuchal tranlucency measurement was 8 mm. No other anomalies were noted at ultrasound. Sonographic follow-up showed a non-septated cystic mass on the posterior aspect of the fetal neck and generalized hydrops. Transabdominal amniocentesis was performed revealing a 45, XO karyotype. After counselling the parents decided to continue the pregnancy. An in utero fetus was identified at 18 weeks of gestation. The pregnancy was terminated and autopsy confirmed CH and fetal hydrops without any other structural anomaly.

Case 2/Case 3

A 24-year-old woman, gravida 3, para 0, abortus 2, and a 21-year-old woman, gravida 1, para 0, were referred to our clinic for routine antenatal care. Their past medical history were unremarkable. There was no family history of congenital anomalies. Diagnosis of CH was made at 14 and 15 weeks of gestation in cases 2 and 3, respectively. Ultrasound of both fetuses revealed thin walled, multiseptate cystic structures posterior to the fetal head and neck eccentrically situated with respect to the long axis of the fetuses. There were no vertebral column defects but both had serosal fluid collection and cutenous edema (Figure 1 a, b). Gestational ages were determined by crown-rump length and they corresponded with the pregnancy duration. A careful sonographic search for other associated congenital anomalies was done. In the follow-up, size of the CH and severity of hydrops increased in both cases. Amniocentesis revealed 45, XO Turner syndrome. Spontaneous fetal demise occured at 21 and 16 weeks of gestation in both cases. Pregnancies were terminated (Figure 1. c, d) and pathological examination confirmed CH and fetal hydrops without any other structural anomaly.

Discussion

CH generally begins to develop between the 6th and 9th weeks of gestation due to failure of the jugular lymphatic sacs to drain into the internal jugular vein, probably resulting in dilatation of the lymphatic sacs into cystic spaces leading to the jugular lymphatic obstruction sequence and hydrops fetalis [4]. It occurs in the neck region in approximately 75% of cases and typically

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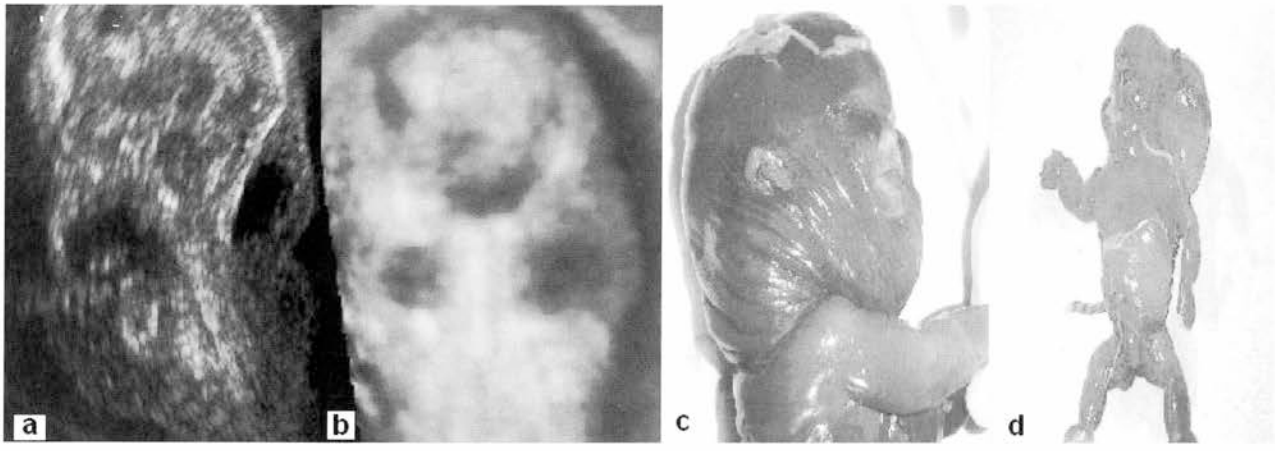

Figure 1. *(a)* — Two dimensional and (b) three dimensional ultrasound image of the fetus with bilateral cystic hygroma at 14 weeks of gestation (case 2); *(c, d)* postabortive pictures of the fetuses with cystic hygroma who developed hydrops at 21 weeks and 16 weeks of pregnancy, respectively.

involves the posterior, lateral rather than anterior portion of the neck as in these three cases. An additional 20% are found in the axilla, while the remaining 5% are found in the mediastinum, retroperitoneum, abdominal viscera, groin, bones and scrotum [5]. The true incidence of CH is unknown. In miscarried fetuses > 3 cm in crown-rump length, the incidence of CH is one in 200 [6].

The diagnosis is usually made by ultrasonography. With this technique CH can be defined as an area of sonolucency in the soft tissue of the occipital region, consisting of two cavities completely separated by a midline septum (nuchal ligament) with or without internal trabeculae (multiseptated or non-septated) [7]. The finding of CH on prenatal ultrasound should prompt a detailed ultrasonographic review of the fetal anatomy to detect structural malformations and signs of fetal hydrops. Particular attention should be directed to the anatomy of the fetal cardiovascular and genitourinary systems and toward detection of fetal hydrops such as fetal skin edema, ascites or pericardial effusions [6]. It is important to differentiate CH from craniocervical masses like encephalocele, other neural tube defects, tumors of the neck such as teratoma or hemangioma, twin sac of a blighted ovum or nuchal edema [3]. This differentiation is possible through the following sonographic features: an intact skull and spinal column, lack of a solid component to the mass, a constant position of the mass relative to the fetal head, and the presence of cysts and septa [6]. In this report in case 1 the CH was non-septated, however in cases 2 and 3 CHs were septated. There were no other associated structural anomalies in any of the three cases.

CH is commonly associated with chromosomal abnormalities in 60-80% of cases [2]. Turner syndrome is the most common as in two of our cases but other chromosomal abnormalities have also been associated with CH including autosomal trisomies, particularly trisomy 21, Klinefelter syndrome, partial trisomies, partial monosomies, translocations and mosaicism [8]. In all of the cases presented here, chromosomal analysis revealed 45, XO karyotype although all were diagnosed in the first trimester. Actually high resolution transvaginal sonography now easily permits recognition of nuchal thickening and cystic hygromas as early as the first trimester [5]. CH has been associated with a number of inherited disorders and malformation syndromes associated with a normal karyotype which include Noonan syndrome, Robert's syndrome, multiple pterygium syndrome and cardiac anomalies. Teratogenic exposure to alcohol, aminopterin and trimethadione has been associated with fetal CH [9]. There are two possible reasons why CH causes fetal hydrops. One is that large cysts have a mass effect which prevents venous return and the other is that protein loss from a cyst can also cause hypoproteinemia of the fetus [2]. All of our three cases developed hydrops. Especially in the second case a mass effect could have been the cause of the hydrops as the mass was large. As indicated before, there is no reliable method for predicting the prognosis and course of the disease. Contemporaneous presence of septations, chromosomal aberrations, fetal hydrops, additional congenital anomalies, size of the CH and gestational age at detection have been suggested to be associated with poor prognosis [10]. None of the 15 fetuses with cystic hygroma survived in the series published by Chervenak *et al.* [11]. However, spontaneous resolution of fetal cystic hygroma with hydrops in Turner's syndrome was reported [12]. Non-diagnostic anomalies indicative of poor prognosis include growth retardation, polyhydramnios and fetal akinesia [6]. Although some studies have suggested that the presence of septations predicts an increased likelihood of aneuploidy and poor prognosis, this has not been a universal finding [13]. In our first case although there were no septations, hydrops developed and the baby died in utero whereas in the second and third cases with septations they had poor prognoses and developed hydrops as well. Hydrops is frequently associated with hygroma. It is associated with an extremely poor outcome and high incidence of chromosomal abnormality; 84-100% of hydropic fetuses have abnormal karyotypes [14]. In this report,

all of the fetuses were hydropic and died in utero soon after developing hydrops, which is in agreement with the literature.

Conclusion

When a prenatal diagnosis of CH is made, determination of the karyotype is recommended in all cases. Serial sonograms to assess the growth of the mass and monitoring for the development of hydrops should aid in management of the pregnancy. In the fetus with associated hydrops, chromosomal abnormality and other major abnormalities, the chance of survival is small and therefore, a non-aggressive approach is advisable. The option of pregnancy termination should be offered before viability.

References

[1] Suwanrath-Kengpol C., Suntharasaj T., Patrapinyokul S., Chanvitan P.: "Prenatal diagnosis of a huge cystic hygroma colli". *Ultr. Obstet. Gynecol.* 2003, *22,* 323.

[2] Ogita K., Suita S., Taguchi T., Yamanouchi T., Masumoto K., Tsukimori K. *et al.*: "Outcome of fetal cystic hygroma and experience of intrauterine treatment". *Fetal Diagn. Ther.*, 2001, *16,* 105.

[3] Nadel A., Bromley B., Benacerraf BR.: "Nuchal thickening or cystic hygromas in first- and early second-trimester fetuses: prognosis and outcome". *Obstet. Gynecol.*, 1993, *82,* 43.

[4] Chitayat D., Kalousek DK., Bamforth J.S.: "Lymphatic abnormalities in fetuses with posterior cervical cystic hygroma". *Am. J. Med. Genet.*, 1989, *33,* 352.

[5] Cohen M.M., Schwartz S., Schwartz M.F., Blitzer M.G., Raffel L.J., Mullins-Keene C.L. *et al.*: "Antenatal detection of cystic hygroma". *Obstet. Gynecol. Surv.,* 1989, *44,* 481.

[6] Gallagher P.G., Mahoney M.J., Gosche J.R.: "Cystic hygroma in the fetus and newborn". *Semin. Perinatol.,* 1999, *23,* 341.

[7] Gembruch U., Hansmann M., Bald R., Zerres K., Schwanitz G., Fodisch H.J.: " Prenatal diagnosis and management in fetuses with cystic hygromata colli". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 1988, *29,* 241.

[8] Bronshtein M., Zimmer E.Z., Blazer S.: "A characteristic cluster of fetal sonographic markers that are predictive of fetal Turner syndrome in early pregnancy". *Am. J. Obstet. Gynecol.,* 2003, *188,* 1016.

[9] Carr R.F., Ochs R.H., Ritter D.A., Kenny J.D., Fridey J.L., Ming P.M.: "Fetal cystic hygroma and Turner's syndrome". *Am. J. Dis. Child.,* 1986, *140,* 580.

[10] Droste S., Hendricks S.K., Von Alfrey H., Mack L.A.: "Cystic hygroma colli: perinatal outcome after prenatal diagnosis". *J. Perinat. Med.,* 1991, *19,* 449.

[11] Chervenak F.A., Isaacson G., Blakemore K.J., Breg W.R., Hobbins J.C., Berkowitz R.L. *et al.*: "Fetal cystic hygroma. Cause and natural history". *N. Engl. J. Med.*, 1983, *309,* 822.

[12] Mostello D.J., Bofinger M.K., Siddiqi T.A.: "Spontaneous resolution of fetal cystic hygroma and hydrops in Turner syndrome". *Obstet. Gynecol.*, 1989, *73,* 862.

[13] Suchet I.B., van der Westhuizen N.G., Labatte M.F.: "Fetal cystic hygromas: further insights into their natural history". *Can .Assoc. Radiol. J.,* 1992, *43,* 420.

[14] Ganapathy R., Guven M., Sethna F., Vivekananda U., Thilaganathan B.: "Natural history and outcome of prenatally diagnosed cystic hygroma". *Prenat. Diagn.*, 2004, *24,* 965.

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