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Case Report

Late-onset fetal bilateral pleural effusions associated with Down syndrome

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ABSTRACT

Objective: We present two cases of late-onset bilateral fetal pleural effusions associated with fetal Down syndrome.

Case reports: **Case 1**. A 33-year-old Vietnamese woman had undergone regular sonographic examinations since 23 weeks of gestation and no abnormality had been noted. However, bilateral moderate pleural effusions were found at 33 weeks of gestation, and massive pleural effusion, ascites and polyhydramnios developed at 34 weeks of gestation. Aspiration of the pleural effusion was subsequently performed. Clinical laboratory surveys of the aspiration fluid excluded toxoplasmosis and cytomegalovirus infection. Cytogenetic analysis of cultured lymphocytes derived from pleural effusion revealed a karyotype of 47,XX,+21. The parents elected to continue the pregnancy. Intrauterine fetal demise occurred at 37 weeks of gestation, and a macerated female baby was delivered. Postnatal cytogenetic analysis of the umbilical cord confirmed the prenatal diagnosis.

Case 2. A 41-year-old Pakistani woman had undergone regular sonographic examinations and no abnormality had been noted. However, isolated bilateral mild pleural effusions were noted at 27 weeks of gestation. Amniocentesis revealed a karyotype of 47,XY,+21 and simultaneous array comparative genomic hybridization analysis of uncultured amniocytes confirmed the diagnosis of Down syndrome. The pregnancy was subsequently terminated.

Conclusion: Fetuses with Down syndrome may present late-onset bilateral pleural effusions. Prenatal diagnosis of late-onset bilateral pleural effusions should raise the possibility of fetal Down syndrome and cytogenetic investigation is warranted.

Introduction

Pleural effusion is defined as fluid accumulation in the pleural space and has been estimated to occur in 1:10000–1:15000 pregnancies [1–3]. However, Hashimoto et al. [4] in a prospective study reported a higher incidence of 1.2% in low-risk obstetric cases at 7–10 weeks of gestation. Fetal pleural effusion can be classified as primary and secondary pleural effusion. Primary fetal pleural effusion is caused by lymphatic vessel anomalies or thoracic cavity defects [5,6]. Secondary fetal pleural effusion includes immune hydrops such as Rh or ABO incompatibility, and non-immune hydrops such as chromosomal abnormalities, congenital cardiac anomalies, genetic disorders, infections, metabolic diseases, and hematologic diseases [6,7].

Here we present two cases of late-onset secondary pleural effusion associated with Down syndrome.

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Case reports

Case 1

A 33-year-old Vietnamese multigravid woman had undergone regular sonographic examinations since 23 weeks of gestation and no sonographic abnormality had been noted. She had not received any Down syndrome screening because of her religious belief. However, bilateral moderate pleural effusions were found at 33 weeks of gestation, and massive pleural effusion, ascites and polyhydramnios developed at 34 weeks of gestation (Figs. 1 and 2). A fetal therapy of thoracentesis was suggested and an aspiration of 80 cc clear yellowish pleural fluid was subsequently made. Clinical laboratory surveys of the aspiration fluid excluded toxoplasmosis and cytomegalovirus infection. Cytogenetic analysis of cultured lymphocytes derived from aspired pleural fluid revealed a karyotype of 47,XX,+21. The parents elected to continue the pregnancy. Unfortunately, intrauterine fetal demise occurred at 37 weeks of gestation, and a macerated 3202 g female baby was delivered. Postnatal cytogenetic analysis of the umbilical cord confirmed the prenatal diagnosis.

Case 2

A 41-year-old Pakistani multigravid woman had undergone regular sonographic examinations and no abnormality had been noted. She refused any prenatal non-invasive or invasive diagnosis of Down syndrome because of her religious belief. However, mild isolated bilateral pleural effusions were noted at 27 weeks of gestation. The risk of chromosome abnormalities was explained to the parents and amniocentesis was suggested. Amniocentesis revealed a karyotype of 47,XY,+21 and simultaneous array comparative genomic hybridization analysis of uncultured amniocytes confirmed a diagnosis of Down syndrome. The pregnancy was subsequently terminated, and a 1900 g male fetus was delivered.

Discussion

The particular aspect of this presentation is the late-onset occurrence of bilateral pleural effusions associated with fetal Down syndrome. Despite the introduction of Down syndrome invasive screening programs and diagnostic procedures, some pregnant women choose to forgo prenatal diagnosis of Down syndrome in early pregnancy. Our cases provide evidence that fetal pleural effusion is an important sonographic marker in late gestation and especially in pregnancies without prior fetal Down syndrome screening and invasive diagnostic procedures in early gestation.

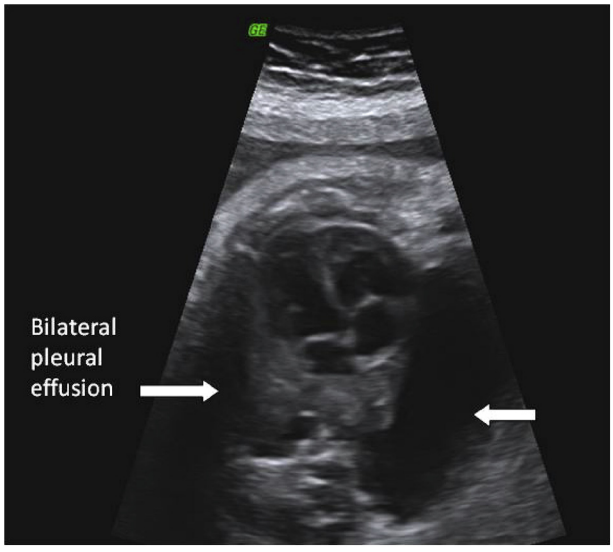

Fig. 1. Prenatal ultrasound of Case 1 at 34 weeks of gestation shows bilateral pleural effusions.

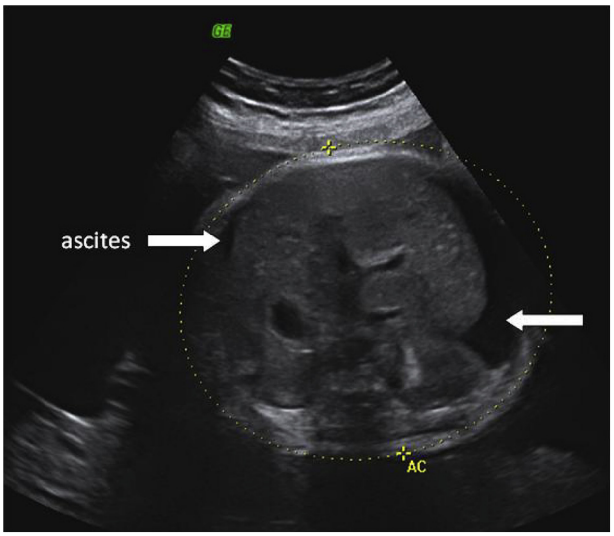

Fig. 2. Prenatal ultrasound of Case 1 at 34 weeks of gestation shows fetal ascites.

The incidence of chromosomal abnormalities associated with fetal pleural effusion has been reported to range from 6.8% to 81.8% (Table 1) [3,4,8–13]. Table 1 shows a higher incidence of chromosomal abnormalities in the first trimester than in the second and third trimester. For example, Hashimoto et al. [4] reported an incidence of 81.8% (9/11) chromosomal abnormalities associated with first-trimester pleural effusion. Conversely, fetal pleural effusion occurring in the second and third trimesters has a lower incidence of chromosomal abnormalities. For example, Blott et al. [9] reported an incidence of 9% (1/11) and Rodeck et al. [10] reported an incidence of 12.5% (1/8) in second-to-third-trimester fetal pleural effusion. According to Table 1, the overall incidence of chromosomal abnormalities associated with fetal pleural effusion is estimated to be 30.9% (148/478). This estimation is similar to the incidence reported by Nicolaides et al. [8], Waller et al. [3] and Ruano et al. [12]. Table 1 also shows that the most common chromosomal abnormality associated with fetal pleural effusion is Turner syndrome which is followed by Down syndrome and Edwards syndrome. The incidence of fetal pleural effusion associated with chromosomal abnormalities has previously been reported in several review studies without complete cytogenetic data. In a review of 124 cases from 38 reports with fetal pleural effusion, Weber et al. [14] reported that at least four cases (3.2%) had Down syndrome. In a review of 82 cases from 31 reports with fetal pleural effusion, Hagay et al. [15] reported that at least four cases (4.9%) had Down syndrome. In a review of 147 cases from three reports and an additional six cases in their study, Achiron et al. [2] reported that at least nine cases (9/153 = 5.8%) had chromosomal abnormalities including one case with Turner syndrome and eight cases with Down syndrome.

The frequency of fetal pleural effusion in fetuses with Down syndrome is approximately 1% [16]. The proposed mechanisms of pleural effusion associated with Down syndrome include lymphatic dysplasia, transient abnormal myelopoiesis (TAM), and alveolar hypoplasia [17–21]. Moerman et al. [17] presented seven cases with bilateral chylothorax of which the perinatal autopsies of all the

Table 1
Reported chromosomal abnormalities associated with fetal pleural effusion.

Authors	Total cases	Gestational age at diagnosis	Cases with karyotyping	Cases with chromosomal abnormalities	Chromosomal abnormalities
Nicolaides et al. (1986) [8]	40	2nd ~ 3rd trimester	40	13 (13/40 = 32.5%)	45,X (n = 6), trisomy 21 (n = 5), and others (n = 2).
Blott et al. (1988) [9]	11	2nd ~ 3rd trimester	11	1 (1/11 = 9.1%)	Trisomy 21 (n = 1)
Rodeck et al. (1988) [10]	8	2nd ~ 3rd trimester	8	1 (1/8 = 12.5%)	Trisomy 21 (n = 1)
Hashimoto et al. (2003) [4]	14	1st trimester	11	9 (9/11 = 81.8%)	45,X (n = 6), trisomy 21 (n = 1), trisomy 2 (n = 1), and triploidy (n = 1).
Waller et al. (2005) [3]	246	1st ~ 3rd trimester	238	84 (84/238 = 35.3%)	45,X (n = 37), trisomy 21 (n = 31), trisomy 18 (n = 6), and others (n = 10).
Klam et al. (2005) [11]	44	1st ~ 3rd trimester	44	3 (3/44 = 6.8%)	45,X (n = 1), triploidy (n = 1), and 92, XXYY (n = 1).
Ruano et al. (2011) [12]	65	1st ~ 3rd trimester	56	23 (23/56 = 41.1%)	45,X (n = 16), trisomy 21 (n = 5), trisomy 18 (n = 1), and 47, XXY (n = 1).
Mallmann et al. (2017) [13]	78	2nd ~ 3rd trimester	70	14 (14/70 = 20%)	Trisomy 21 (n = 14)
Total	506		478	148 (148/478 = 30.9%)	45,X (n = 66), trisomy 21 (n = 58), trisomy 18 (n = 7), and other (n = 17).

cases revealed pulmonary lymphangiectasis (PL), which suggested that PL may be part of multiple congenital anomalies syndrome. Ochiai et al. [18] reported a case with Down syndrome and hydrops fetalis in which postnatal lymphoscintigraphy and histopathology necropsy revealed a diagnosis of systemic lymphatic dysplasia. TAM has been reported in 10% of newborns with Down syndrome [22]. Hojo et al. [19] reported seven cases of TAM with Down syndrome and suggested that the causes of hydrops fetalis may include anemia-related cardiac failure, hepatomegaly, hypoalbuminemia, and portal venous hypertension. Cooney and Thurlbeck [20] studied seven cases with Down syndrome and autopsies; all were found to have had alveolar hypoplasia with a relatively small alveolar surface area. Modi and Cooke [21] further assumed the relatively small alveolar surface area may delay the clearance of lung fluid and predispose to pleural effusion.

The characteristics of fetal pleural effusion associated with Down syndrome appear late-onset gestation [13,23] with no other sonographic abnormalities [3]. Yumoto et al. [23] compared 287 primary fetal pleural effusions caused by lymphatic leakage with 91 fetal pleural effusions associated with Down syndrome, and they found that the mean gestational age at diagnosis was later in the Down syndrome group (27.5 ± 5.6 weeks vs 29.2 ± 3.7 weeks) among which only 28 cases (28/91 = 30.8%) were diagnosed before delivery. Mallmann et al. [13] compared 64 primary fetal pleural effusions with 14 fetal pleural effusions associated with Down syndrome, and found that the mean gestational age at diagnosis was significantly later in Down syndrome group (24.2 ± 4.6 weeks vs 29.8 ± 3.3 weeks). Waller et al. [3] reported 246 fetal pleural effusions, among which 238 cases had chromosomal studies and 92 cases had isolated pleural effusion; they found 84 cases (84/238 = 35.3%) had abnormal karyotype including Turner syndrome (n = 37) and Down syndrome (n = 31). In the 84 cases with chromosomal abnormalities, 73 cases had multiple sonographic abnormalities and 11 cases had only isolated fetal pleural effusion. In their study, all the 37 cases with Turner syndrome had multiple sonographic abnormalities and among the 11 cases with isolated fetal pleural effusion, six had Down syndrome, two had unbalanced translocations, one had of Edwards syndrome, one had mosaic trisomy 20, and one had pericentric inversion of chromosome 16. Waller et al. [3] found that 54.5% (6/11) of the cases with both chromosomal abnormalities and the isolated pleural effusion group had Down syndrome, and they concluded that Down syndrome was the most common chromosomal abnormality associated with isolated fetal pleural effusion.

In summary, we presented two cases of late-onset bilateral fetal pleural effusions associated with fetal Down syndrome. Fetuses with Down syndrome may present late-onset bilateral pleural effusions. Prenatal diagnosis of late-onset bilateral pleural effusions should raise the possibility of fetal Down syndrome and subsequent cytogenetic investigation is warranted.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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