Autopsy findings in fetuses with cystic hygroma: a literature review and our center's experience

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Summary

Purpose of investigation: To report our experience of autopsied cases of fetal cystic hygroma (CH) and discuss the role of fetal autopsy in genetic counseling. *Methods:* A review of autopsy reports at our institution revealed 18 cases of fetal CH over a 10-year period (from 2000 to 2010). The clinical data, results of cytogenetic analysis and prenatal ultrasound findings were also retrieved and compared to the autopsy findings. *Results:* Fetal death was due to intrauterine death in eight cases, therapeutic abortion in eight cases and spontaneous abortion in two cases. Cytogenetic analysis was available in 12 cases, and the results showed an abnormal karyotype in seven cases (5 cases of Turner syndrome and 2 cases of trisomy 21). The mean size of CH was 5.4 cm. Other malformations or findings suggestive of the cause of fetal death were diagnosed in 10/18 cases (55.6%). The most common autopsy findings were hydrops and central nervous system anomalies. The autopsy findings were in agreement with the prenatal ultrasound findings in 13/18 cases (72.2%), while in five cases (27.8%) additional findings were detected during autopsy. The most common placental abnormalities were infarcts and calcifications. *Conclusion:* In addition to prenatal diagnostic studies, fetal autopsy and pathologic examination of fetal and placental tissues may help to establish the exact cause of death and disclose important information as to the presence of various fetal malformations or placental abnormalities.

Key words: Rat; Autopsy; Cystic hygroma; Fetus; Genetic counseling; Malformations.

Introduction

Lymphangiomas are rare congenital benign lesions of the lymphatic system, which are composed of cystically dilated vascular channels lined by inconspicuous endothelial cells and filled with lymph fluid [1]. Although the debate as to their exact nature has not yet been settled, the belief that most lymphangiomas represent benign malformations of the lymphatic system arising at sites of lymphatic-venous connections, rather than true neoplasms, is the prevalent one [2]. Furthermore, despite the persisting controversy regarding the exact origin and pathogenesis of these lesions it is also generally agreed that their development is closely related to the maturation of the lymphatic system while several different theories attempting to explain the mechanism of their formation have been proposed [1]. Sequestration of lymph tissue, abnormal budding of lymph vessels, lack of fusion with the venous system or obstruction of lymph vessels are all discussed as causes of lymphangiomas, while various factors such as trauma, infection, chronic inflammation or obstruction during embryonic development are considered as potential triggers of this process [1, 3-7].

The most commonly used classification of lymphangiomas separates them into three major forms: capillary, cavernous and cystic [1, 2, 7]. The latter (cystic) form has been traditionally known as cystic hygroma (CH) [2] and accounts for approximately 90% of the lymphangiomas in the head and neck [8], although it may also occur at various other sites including the axilla, mediastinum, abdomen and retroperitoneum [9, 10]. This observation has also led to the concept that CH should be defined merely as a lymphangioma located in the head and neck region, where the formation of a cystic lesion is encouraged by the presence of loose fascia [9].

We present a brief review of the literature related to CH and further discuss the role of fetal autopsy in genetic counseling. The clinical and autopsy findings in 18 cases of fetal CH diagnosed in our center are also presented.

Materials and Methods

A search of autopsy reports at our institution (Pathology Laboratory of Areteion University Hospital) revealed 18 cases of fetal CH over a 10-year period (from 2000 to 2010). Postmortem examination of the fetuses was done according to a predesigned protocol including a photograph, skeletal radiography (in cases of suspected skeletal anomalies), and a thorough external and internal examination and microscopic evaluation of fetal tissue as per autopsy findings on gross examination. Histopathologic examination of placental tissue was also carried out when the placenta was available. All fetal autopsies were performed only after obtaining a written consent from the parents. The clinical data, prenatal ultrasound and cytogenetic findings were retrieved from the files of the 2nd Obstetrics and Gynecology Clinic of our hospital and compared to the autopsy findings. Cytogenetic analysis was performed in 12/18 cases (66.7%). The results revealed an abnormal karyotype in 7/12 cases (58.3%), i.e., Turner syndrome in five cases and trisomy 21 in two cases.

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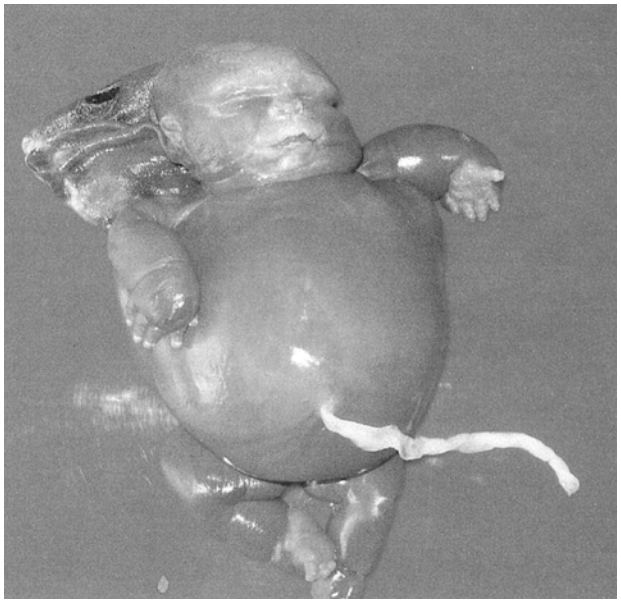

Figure 1. — Hydropic fetus (32 weeks of gestation) presenting a cervical cystic lymphangioma measuring 12 cm (case 1).

Results

The clinical data, the results of cytogenetic analysis and the outcome of our studied cases are presented in Table 1, while the autopsy findings and the placental histopathologic features are summarized in Table 2. The maternal age ranged from 20- 40 years (mean 28.6 years), while the gestational week at the time of fetal loss ranged from 13-32 weeks (mean 20.2 weeks). Fetal death was due to intrauterine death in eight cases, therapeutic abortion in eight cases and spontaneous abortion in two cases. The size of CH ranged from 1-12 cm (mean 5.4 cm) (Figure 1). Aside from CH, other structural malformations or findings suggestive of the cause of fetal death were diagnosed in 10/18 cases (55.6%). The most common autopsy findings were hydrops and central nervous system anomalies. The autopsy findings were in agreement with the prenatal ultrasound findings in 13/18 cases (72.2%), while in five cases (27.8%) additional findings were detected during autopsy examination of the fetus and subsequent histological examination of fetal tissue. The additional autopsy and/or histologic findings were: intrauterine pneumonia (case 2), syndactyly of the 3rd and 4th digits of the right hand (case 3), cystic pulmonary malformation (case 5), villous hyperplasia of choroid plexus and polycystic kidneys (case 11). Fibular aplasia was also diagnosed on postmortem X-ray in one case (case 11).The placenta was available in 13/18 cases (72.2%). Histopathological examination of placental tissue was consistent with normal findings in 6/13 cases (46.2%) , while in the remaining seven cases (53.8%) various placental abnormalities were diagnosed, i.e., multiple infarcts (cases 5, 8, 10 and 12), extensive calcifications (cases 5, 7, 13), retroplacental hematoma (cases 10 and 11), acute chrioamnionitis (case 7) and chronic placentitis (case 5). In the latter case, suspicion of a specific infection, such as toxoplasmosis, was raised.

Table 1. — *Clinical data, cytogenetic analysis and outcome*.

Case	Maternal age (years)	Gestational age (weeks)	Karyotype	Outcome formation
1	27	32	NA	TA
2	26	20	45XO	ID
3	24	19	46XX	ID
4	30	18	47,T21	TA
5	24	19	NA	ID
6	24	21	46XX	ID
7	40	15	NA	ID
8	26	23	46XY	ID
9	27	20	45XO	SA
10	22	19	NA	TA
11	32	21	NA	TA
12	32	30	46XY	ID
13	35	16	NA	SA
14	38	13	47,T21	TA
15	36	19	46XX	ID
16	22	20	45XO	TA
17	30	20	45XO	TA
18	20	19	45XO	TA

NA: not available, TA: therapeutic abortion, ID: intrauterine death, SA: spontaneous abortion.

Table 2. — *Autopsy and placental histopathologic findings*.

Cases	Autopsy Findings (gross and histologic)	Placental histopathology
1	CH (12 cm), hydrops	Normal
2	CH (10 cm), hydrops, intrauterine pneumonia	NA
3	CH (3 cm), syndactyly of 3rd and 4th digits (right hand)	Normal
4	CH (8 cm)	Normal
5	CH (10 cm), cystic pulmonary malformation	Chronic placentitis, multiple infarcts, extensive calcifications
6	CH (6 cm), nuchal cord	Normal
7	CH (1 cm)	Acute chorioamnionitis, extensive calcifications
8	CH (3 cm)	Multiple infarcts
9	CH (3 cm), findings consistent with Turner syndrome	NA
10	CH (7 cm), meningo-myelocele, spina bifida	Multiple infarcts, retroplacental hematoma
11	CH (8 cm), hydrops, cardiac & pulmomary hypoplasia, cerebellar hypoplasia, villous hyperplasia of choroid plexus, polycystic kidneys, fibular aplasia*	Placental hydrops, retroplacental hematoma
12	CH (3 cm)	Multiple infarcts
13	CH (2 cm)	Extensive calcifications
14	CH (1 cm)	NA
15	CH (2 cm)	NA
16	CH (7.5 cm), hydrops	Normal
17	CH (4 cm), hydrops	Normal
18	CH (7 cm), hydrops	NA

* Postmortem X-ray finding

Discussion

CH typically develops in utero late in the first trimester to early in the second trimester and, due to the widespread use of prenatal sonography, is often detected prenatally by ultrasound [11, 12]. Although complete surgical excision remains the treatment of choice, especially when the anatomic position of the mass causes concern for potential airway compromise, and is usually effective in eliminating the defect, spontaneous regression of this lesion may occasionally occur [13, 14]. Furthermore, nonsurgical therapies such as sclerotherapy or even a non-interventional approach (watchful waiting) have been recently proposed as alternative options to surgery in selected cases to avoid the surgical risk of recurrence or nerve damage [15, 16]. Nevertheless, many of the fetuses with CH also have a variety of additional malformations, commonly associated with an underlying chromosomal anomaly, most frequently Turner syndrome but also trisomy 21 or other genetic disorders [2, 12]. For this reason, the overall prognosis for babies with a prenatal diagnosis of CH is poor, with a fatal outcome for the majority of cases [12, 17, 18]. Cytogenetic analysis is an indispensable diagnostic tool in the overall evaluation of fetuses with CH, and should be always included in the diagnostic work-up of these cases, as it may confirm the presence of a chromosomal abnormality thus allowing for the option of termination of pregnancy, and provide valuable information for genetic counseling [19]. In line with previous reports [11, 13, 17-19], Turner syndrome was the most common chromosomal abnormality among our studied cases with available cytogenetic analysis.

Additional malformations are often disclosed during postmortem examination of fetuses with prenatally diagnosed anomalies, thus leading to the adjustment of the prenatal diagnosis [20, 21]. In addition to establishing the exact cause of death, fetal autopsy is therefore the sole diagnostic method able to confirm, clarify, extend, or even contradict the prenatal diagnostic studies [20-22]. The value of fetal autopsy as an adjunctive tool in genetic counseling has been well established, and a review of the literature reveals several previous studies and literature reviews evaluating the role of autopsy in fetuses with chromosomal abnormalities or structural malformations [20, 23-29]. These studies have emphasized the importance of fetal autopsy in providing an accurate etiologic diagnosis necessary for genetic counseling. Boyd *et al*. recently reported that in cases of terminated pregnancies because of anomalies which were prenatally diagnosed by ultrasound, by declining an autopsy, parents will remain ignorant of information that might change the recurrence risk in one of four cases and have a one in 13 chance for missing confirmation of a high (one in four) recurrence risk [23]. In another large series of 328 fetuses by Amini *et al*. [24], comparing the ultrasound and autopsy findings in pregnancies terminated after sonographic detection of fetal anomalies, the authors found that fetal autopsy provided further diagnostic information in 47% of their studied cases, thus concluding that fetal autopsy is essential for a definitive diagnosis. In a similar comparative study by Ramalho *et al*. [25], additional information after fetal autopsy was obtained in 26.3% of cases, including major structural anomalies in almost half of these cases. In a study of 288 second-trimester abortions because of malformations detected on prenatal ultrasound, discrepancies were noted between sonographic and autopsy findings in about 40% of pregnancies, and the authors concluded that termination of pregnancy should be followed by autopsy [30]. Consistent with these results are also the findings of several other studies [20, 26-29]. Dickinson *et al*. [29] who also found that fetal autopsy may provide significant information and/or clarify some prenatal findings, further stressed that the currently observed decline in fetal autopsy rates may lead to a loss of significant diagnostic and recurrence risk-counselling information. Needless to say of course that adequate and reliable access to the clinical data, and the prenatal ultrasound and cytogenetic findings is of paramount importance in designating the appropriate autopsy strategy [31, 32]. As reported by Tennstedt *et al*. [33], the use of an interdisciplinary database, including the prenatal, molecular-cytogenetic, X-ray and autopsy findings in a specialized center of perinatal medicine, may facilitate the identification of very small or rare malformations, thus significantly improving the quality of genetic counseling.

The autopsy findings in cases of fetal CH have been previously reported in a limited number of studies or only as reports of rare cases [17, 34-37]. In the largest series (57 cases) of autopsied CH cases published, to the best of our knowledge, the authors noted that autopsy findings showed various malformations associated with CH, especially hydrops, craniofacial and extremity anomalies and cardiac abnormalities [34]. In another series of 17 cases of fetal CH, hydrops was also the commonest autopsy finding [35]. Carson *et al*. [37] further reported that the diagnosis of CH was missed on prenatal ultrasound in four of 13 autopsied cases with available ultrasound examinations, while histopathologic examination of the lesion allowed the recognition of lymphatic vascular architecture and the demonstration of immunoreactivity of the endothelium to factor VIII regardless of the degree of autolysis. In our present study postmortem examination revealed additional malformations not apparent on prenatal ultrasound and contributed in the clarification of the exact cause of death in a significant percentage (40%) of cases. In line with the aforementioned previous reports [34, 35], hydrops was the most common abnormality associated with CH in our series as well.

With the notable exception of renal cystic disease, whose adequate diagnosis and classification requires microscopic evaluation of fetal tissue sections [20, 23], the value of histological examination of fetal organs in the presence of structural malformations remains rather controversial. It has been previously supported that histological analysis is unlikely to be helpful in providing significant information as regards the cause of fetal loss, or any predictions for future pregnancies, mainly because abnormal histological findings may be the result of

intrauterine fetal death and not necessarily the cause [20, 38]. On the other hand there is also the view that histological examination of all major organs of the fetus is an important diagnostic tool and should always be undertaken [22, 28, 39, 40]. Although histopathological examination of any fetal organ may yield diagnostically valuable information, the most important histopathological findings are frequently retrieved in the central nervous system, the skeletal system and the kidneys [39]. It should also be kept in mind that in dilation and evacuation specimens of aborted fetuses a regular autopsy procedure may be impossible due to the inevitable fragmentation, therefore histological examination in these cases may enable confirmation of the antenatal diagnosis [22, 39]. Furthermore, as rightly pointed out by Millar and Fothergill [41], routine histological examination of fetal tissue may be particularly valuable in units with limited experience in prenatal ultrasound or lack of adequate imaging equipment. Another major benefit of histological examination of fetal tissue is the storage of fetal genetic material, which may be used for the performance of molecular biological studies and the identification of known or suspected genetic diseases either in the present or in the future [42].

In accordance with a previous autopsy study of fetuses with congenital malformations [20], multiple placental infarcts were the most common placental abnormality in our studied cases. Despite the fact that the value of placental examination in clarifying the cause of intrauterine fetal death remains the object of significant controversy, especially in the concomitant presence of fetal anomalies, placental abnormalities are well established causes of fetal demise and should be always evaluated in association with the remaining findings [43]. As previously emphasized, the placenta is a maternal-fetal organ mirroring fetal disease, and its pathologic examination may provide valuable information in genetic and infectious diseases of the fetus [39]. Histological examination of grossly apparent placental abnormalities may also help to determine the age of the lesion, as in the presence of hematomas attached to the chorion or placenta or within the placental tissue, thus clarifying their relation to a potential iatrogenic injury during the procedures undertaken for sampling [22]. In previous studies placental abnormalities have been associated with conditions causing fetal hydrops [44, 45]. It has also been previously claimed that placental infarcts may represent a major causal factor of fetal death, and an association of placental infarction with prenatal brain damage has been suggested [46-48]. However, other researchers have stated that only massive placental infarction should be considered as an obvious presumptive cause for fetal demise and that placental infarcts have been documented in live and completely normal births as well, and advice for caution as regards any claim that a particular placental lesion has been the direct cause of fetal demise without prior strict evaluation of all the possible factors which could have directly led or contributed to the adverse pregnancy outcome [43]. Previous reports have also revealed that in fetuses with genetic disorders or structural malformations the placenta generally shows nonspecific abnormalities, such as villous immaturity or edema, that are not particularly helpful in establishing a diagnosis [39].

In conclusion, autopsy examination of fetuses with structural malformations such as CH may be of value in revealing additional anomalies not necessarily apparent on prenatal imaging studies and aid in the identification of the exact cause of death. "The family seeks and deserves answers regarding the cause of the loss of a baby" [20] and fetal autopsy may also provide evidence for these answers. On the other hand, as rightly pointed out by Boyd *et al*. [23], parents should also be fully informed prior to giving their consent for an autopsy examination about the procedures involved and about the benefits in providing information about risks of recurrence.

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