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First case of liposarcoma arising from the fallopian tube: Case report and review of the literature

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Abstract

Liposarcoma is the most common soft tissue sarcoma in adults, and it typically occurs in either the retroperitoneum or the extremities. However, this malignant tumor is very rare in the female reproductive system. A 58-year-old woman presented with acute abdominal pain, and computed tomography (CT) scan detected multiple masses measuring 4–6 cm in size with a fatty density in her adnexal region. Laparoscopic evaluation revealed tumors of the left fallopian tube with a normal left ovary. Histopathological evaluation of the resected pelvic tumors showed lipocytes and lipoblasts of various sizes, leading to diagnosis of well-differentiated liposarcoma of the left adnexal region. This is the first known case of a liposarcoma arising from the fallopian tube. When a pelvic mass with fatty density that does not show typical findings of a mature cystic teratoma is detected by either CT or magnetic resonance imaging, the possibility of a liposarcoma should be considered.

Key words: fallopian tube, liposarcoma, mature cystic teratoma.

Introduction

Liposarcomas, which account for at least 20% of all sarcomas in adults, typically occur in either the retroperitoneum or the lower extremities. However, in the gynecological field, there have been very few reports of either retroperitoneal liposarcoma or intra-abdominal liposarcoma. To date, although several cases of liposarcoma from the uterine body have been reported, there is no case of a liposarcoma occurring in the adnexal region.

We report here the first known case of liposarcoma arising from stroma of the fallopian tube, which we mistakenly diagnosed to be a mature cystic teratoma before operation.

Case Report

A 58-year-old woman was transferred to our hospital due to acute onset of lower abdominal pain. She was taking medication for hypertension and diabetes mellitus, but was otherwise in good health prior to the onset of abdominal pain. A pelvic examination revealed severe tenderness in the left adnexal region, but a pelvic mass was not palpable. A complete blood count showed leukocytosis. Chest X-ray and electrocardiogram (ECG) findings were both normal. Emergency computed tomography (CT) scan of the abdomen detected multiple pelvic masses measuring 4–6 cm in size with a fatty density (Fig. 1a). In addition, magnetic resonance imaging (MRI) showed heterogeneous masses with a high signal intensity on T_1-weighted and T_2-weighted images (Fig. 1b–d). She was initially diagnosed with probable torsion of ovarian mature cystic teratomas, which are the most common ovarian neoplasms.

Laparoscopic surgery was carried out to remove the pelvic masses. Although no ascites was seen in the abdominal cavity, a normal left ovary and three yellowish smooth masses, with pedicles originating from the

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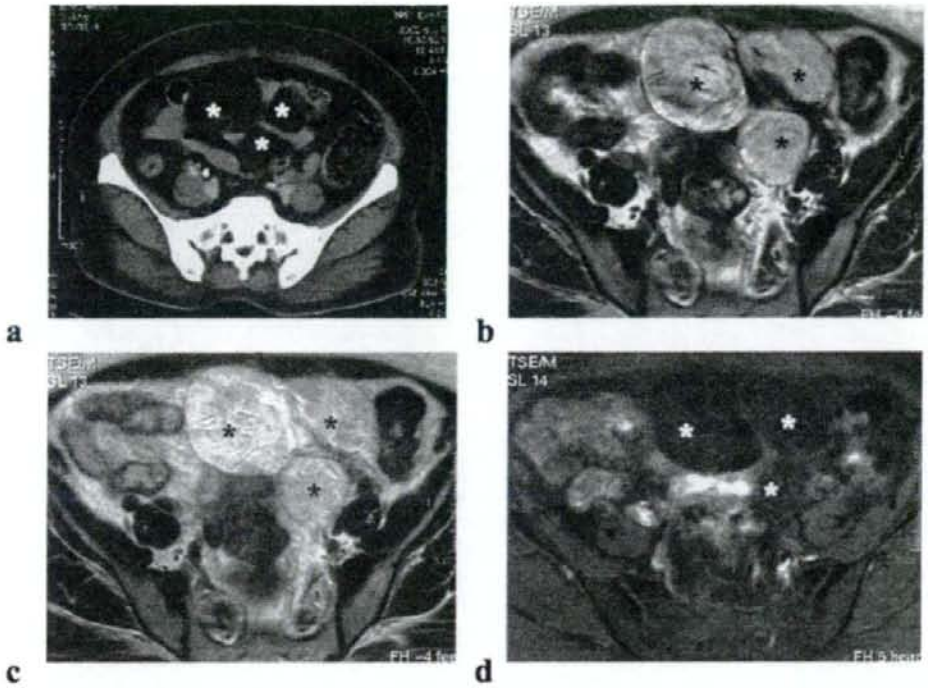

Figure 1 Computed tomography (CT) and magnetic resonance imaging (MRI) findings of liposarcoma. (a) White asterisk indicates one of the heterogeneous masses with fat density in the pelvic cavity detected by CT examination. (b) Black asterisk denotes well-defined masses with a high intensity by both T_1-weighted images of an MRI examination. (c) Black asterisk denotes well-defined masses with high intensity based on T_2-weighted images of an MRI examination. (d) White asterisk shows the masses with a low signal intensity based on T_1-weighted images with fat suppression.

left fallopian tube, were detected. These pedicles, consisting of three masses, had become intertwined with each other, thus most likely being the cause of the patient's abdominal pain. As the cut-surface appearance of these tumors, which we first resected by laparoscopic surgery, comprised a yellowish fatty and grayish white lobulated solid mass, malignant tumors were suspected even though the pelvic masses were not ovarian tumors (Fig. 2a,b). We therefore changed from laparoscopic surgery to a laparotomy in order to perform a complete resection, in addition to a total hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, and peritoneal washing cytology as the treatment for tubal cancer. No biopsies of the lymph nodes or peritoneal regions were carried out because no lymph node swelling or peritoneal dissemination was detected during the operation.

Pathological evaluation of the resected specimen showed the presence of well-differentiated liposarcoma, which was characterized by the proliferation of mature fat cells whose size ranged from small to large, and lipoblasts, which contained multiple vacuoles in the cytoplasm with enlarged, irregular, dense nuclei in fibrous tissue. The collagenous stroma was congested due to torsion of the pedicle (Fig. 3a,b). The resected tumors were diagnosed to be well-differentiated liposarcoma from the stroma including a tela subserosa between the lamina propria mucosae and tunica serosa (Fig. 3c). The mucosa of the fallopian tube was intact. The resection margin was negative and no metastasis was seen in any other specimens. An immunohistochemical study indicated that vimentin and S-100 protein were positive, whereas CD68 was negative. No malignant cells were observed in any peritoneal washing cytology specimens.

Neither chemotherapy nor any other adjuvant therapies were added, because the masses were considered

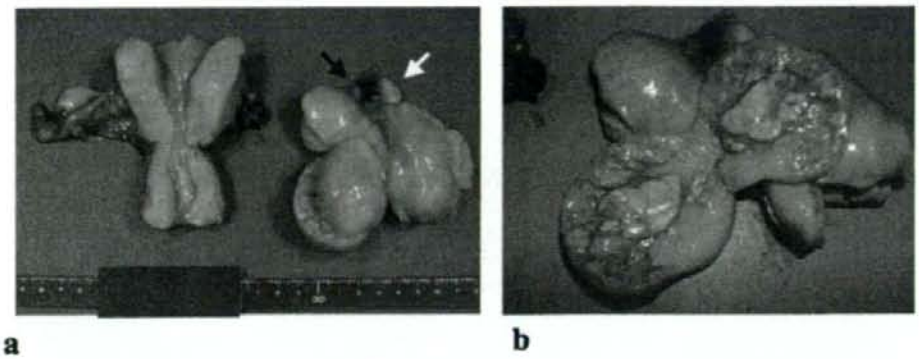

Figure 2 Macroscopic findings of the specimen. (a) Resected masses, uterus and bilateral adnexas. Black arrow indicates the fallopian tube and the white arrow indicates the left ovary. (b) The cut-surface appearance of the tumor was composed of a yellowish fatty and grayish-white lobulated solid mass.

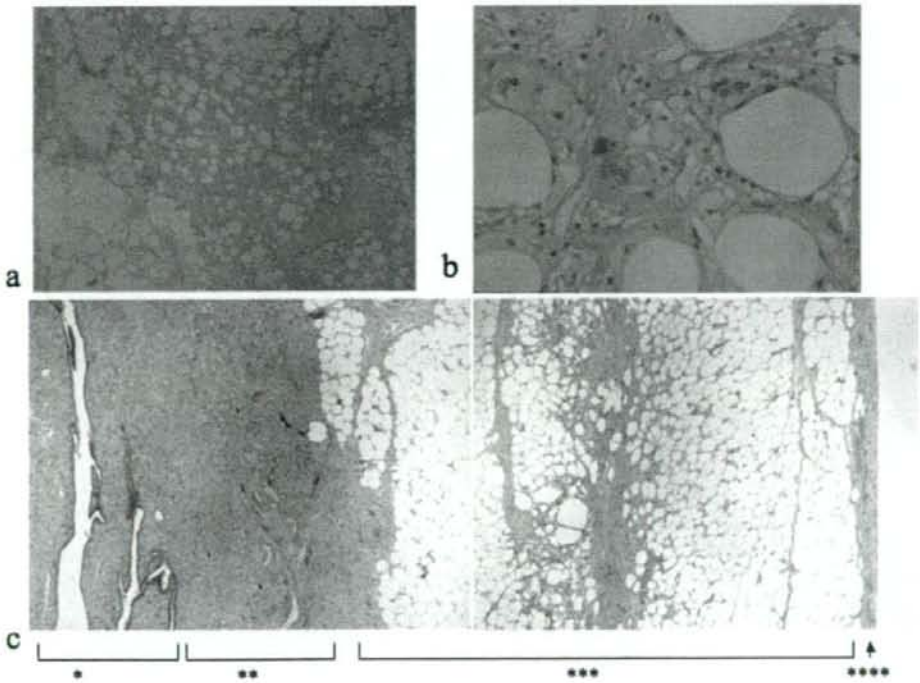

Figure 3 Pathological findings of liposarcoma arising from the stroma of the fallopian tube. (a) Low-power view of the tumor showing mature fat tissue and proliferation of fibrous tissue; H&E, original magnification ×40. (b) High-power view of the tumor cells. Several mature lipocytes and lipoblasts with vacuoles in the cytoplasm, enlarged hyperchromatic nuclei and prominent nucleoli were found. H&E, original magnification ×400. (c) Low-power composition view of the resected tumors which arose from the stroma of the fallopian tube showing the area of the epithelium (*), stroma (**), liposarcomas (***) and serosa (****) of the fallopian tube. H&E, original magnification ×40.

to have been adequately resected. The patient remains disease free 22 months after the surgery.

Discussion

The presence of a fatty component in pelvic masses usually indicates a mature cystic teratoma, as they are the most common ovarian neoplasm found in women. However, the possibilities of fat necrosis, carcinosarcoma or liposarcoma should also be considered. In particular, a small number of cases of retroperitoneal liposarcoma or intra-abdominal liposarcoma have been reported and, therefore, pelvic masses with a fatty component should be managed as potentially malignant tumors. The CT and MRI findings in our patient showed three distinct masses consisting of fat with septations, which are characteristic of well-differentiated liposarcoma.[1] We therefore could have made a diagnosis of liposarcoma before the operation if we had included the possibility of liposarcoma in the differential diagnosis. The poor prognosis of liposarcoma depends on several factors including age older than 60 years, tumor size greater than 5 cm, and high-grade histology.[2]

The histological cell type of liposarcoma, which is classified as being either well differentiated, myxoid/round cell, pleomorphic, or dedifferentiated, is the most important factor predicting survival rates for cases of liposarcoma. The 5-year survival rate for well-differentiated subtypes is 90%, whereas myxoid liposarcomas have a 5-year survival probability of 70–90% and both round cell liposarcoma and pleomorphic liposarcoma have a high metastatic potential and a 5-year survival probability of only 20–50%.[3] According to the American Joint Committee (AAJC) staging protocol for sarcoma of the soft tissue, the stage is determined by the histological grade, the presence of lymph node metastasis and distant metastasis, the tumor size and its location.[4] In this case of a 58-year-old woman, the tumor was an intra-abdominal mass measuring more than 5 cm in size but without any metastasis, and the histological grade of the tumor was a low grade (well-differentiated type). Therefore, this case was classified as stage I disease by AAJC staging and stage Ia by FIGO staging.

The recommendation of the National Cancer Institute for the treatment of adult soft tissue sarcoma of patients with stage I disease is surgical excision. If the tumor is unresectable, preoperative radiation therapy and/or postoperative radiation therapy may be used. In addition, chemotherapy is not carried out in cases of tumors with a low metastatic potential.[5] In the present case: (i) a total hysterectomy, a bilateral salpingo-oophorectomy and a partial omentectomy were all carried out; (ii) no metastases were detected by chest X-ray, CT and MRI examinations; (iii) the peritoneal washing cytology findings were negative; and (iv) her histological diagnosis was well-differentiated liposarcoma with a minimal metastatic potential. Accordingly, neither radiation therapy nor chemotherapy was carried out as adjuvant treatment. She is being followed up clinically and by serial chest X-rays and CT scans of the chest, abdomen and pelvis, and no relapse of symptoms has been observed.

This is the first reported case of liposarcoma arising from a fallopian tube. As the normal treatment protocol for tubal cancer was selected, we performed a total hysterectomy, a bilateral salpingo-oophorectomy and a partial omentectomy for the liposarcoma arising from the stroma of the fallopian tube.

When multiple pelvic masses with a fatty density are detected by either CT or MRI examinations which do not correspond to the typical findings of mature cystic ovarian teratomas, then the possibility of a liposarcoma should be taken into consideration and included in the differential diagnosis.

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Management of prenatal ovarian cysts

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Spontaneous resolution;
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Abstract

Objectives: The aim of the present study was to analyze the antenatal and postnatal outcome of fetal ovarian cysts in relation to their ultrasonographic pattern and size.
Methods: Sixteen fetal ovarian cysts were diagnosed in 16 fetuses and followed with serial ultrasonograms in utero and after birth until spontaneous or surgical resolution.
Results: Eleven fetal ovarian cysts were simple cysts at first prenatal scan but 3 of the 11 became complex cysts at last prenatal scan and required postnatal laparoscopic surgery. Seven of the 11 simple cysts (63%) disappeared on follow-up imaging by ultrasonograms or MRI during pregnancy or within 2 months after birth. The rate of spontaneous resolution of simple cysts was higher than that of complex cysts (40.0%). The mean maximum diameter of the ovarian cysts before delivery that were subsequently excised surgically at postnatal period (50 ± 13.4 mm) was not different from that of ovarian cysts that resolved spontaneously (42.8 ± 12.8 mm, $P = 0.2918$).
Conclusion: In our study, cyst size did not predict the risk of ovarian loss. The opportunity of laparoscopic exploration versus conservative management needs to be investigated because some complex cysts resolved spontaneously in the postnatal period.

1. Introduction

The rate of detection fetal ovarian cysts has increased since the advent of routine antenatal sonography [1]. The etiology of fetal ovarian cysts is not entirely clear. Maturation of the hypothalamus–pituitary–ovary axis commences from the 29th week of gestation under elevated levels of fetoplacental estrogen [2]. An immature hypothalamus–pituitary–ovarian feedback is thought to be responsible for gonadal hyperstimulation in premature fetuses. After delivery, reduction in hormonal stimulation can lead to spontaneous resolution of the ovarian cyst; therefore, a conservative management of uncomplicated cysts has been suggested, although some cysts carry the risk of subsequent complication that might require postnatal surgery [3–5]. Various complications of ovarian cysts have been described, such as compression of neighboring viscera, rupture of the cyst, hemorrhage and ovarian torsion [6–9]. However, there is no standard treatment of fetal ovarian cysts and their management varies widely among different centers. The present retrospective study

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was conducted to analyze the antenatal and postnatal outcome of fetal ovarian cysts in relation to their ultrasonographic pattern and size.

2. Materials and methods

A total of 16 fetal ovarian cysts were diagnosed in 16 fetuses between 30 and 37 weeks of gestation on routine sonography conducted between 1989 and 2006 in our hospitals. The detection of a cystic structure in the fetal abdomen with otherwise normal anatomy of the gastrointestinal and urinary tracts in a female fetus was highly suggestive of an ovarian cyst. This assumption was based on the following fact: other anomalies that can be mistaken as ovarian cysts, such as mesenteric cysts, urachal cysts, enteric duplication, and dilated bowel, are very rare. The shape of enteric bowel duplication is generally tubular, and the difference is a two layered muscle wall seen on antenatal ultrasonography in bowel duplication. But duplications of the gastrointestinal tract are mimick fetal ovarian cysts. Duodenal atresia has a typical double bubble appearance. In cases with a suspected ovarian cyst, a thorough sonographic assessment with/without MR imaging of the entire fetus was performed to exclude other associated anomalies.

The cysts were classified as either complex or simple according to Nussbaum et al. [1]. A cyst that was completely anechoic and had a thin wall was defined as simple, while an echogenic cyst was defined as complex (Fig. 1). We measured the maximum antenatal size of the ovarian cyst, and the associated complications and outcome.

After diagnosis, the mothers were followed by serial ultrasound scans every 2 weeks until delivery, and the newborn was followed postnatally until spontaneous resolution or surgical excision. Spontaneous vaginal delivery took place in all cases except when cesarean section was indicated for obstetrical reasons not related to the fetal ovarian cyst. All study protocols were approved by the Committee for Ethical Issues on Human Genome and Analysis of Nagasaki University.

3. Results

The mean diameter of the 16 fetal ovarian cysts was 42.6 ± 12.3 mm (±SD) at diagnosis. All cysts were first detected in the third trimester. Eleven fetal cysts were simple and five were complex when first detected. All 16 fetuses were born at term, with 14 by normal vaginal delivery and 2 by Cesarean section because of breech presentation or cephalopelvic disproportion.

Spontaneous resolution during pregnancy was noted in 2 of the 11 (18.2%) simple cysts. Five simple cysts diminished in size 6 months after delivery and 4 of these 5 disappeared spontaneously within 2 months after birth, while surgery was performed for enucleation of one simple cyst due to its large size (62 mm) at last prenatal diagnosis (Table 1, Case 3). We didn't aspirate for this case because we took into consideration the possibility of fetal ovarian tumor. Histopathological examination of this cyst showed a simple cyst with no specific epithelial findings.

With regard to the remaining 4 (36.4%) simple cysts, their size did not change or increase at late pregnancy. Three of these simple cysts that did not change in size became the complex type during the prenatal follow-up scans. Repeat sonograms showed a fluid level in the cyst or a solid pattern. Accordingly, surgery was performed within 10 months after birth due to suspected torsion or hemorrhage (Table 1). One of these three cysts showed evidence of torsion at surgery (Table 1, Patient 9) and histopathological examination indicated a necrotic simple cyst with calcification. The other two cysts showed evidence of intracystic hemorrhage but not that of torsion (Table 1, Patients 10 and 11). Histopathological analysis indicated two simple cysts with bleeding with or without calcification. One simple cyst that increased in size later showed spontaneous resolution within

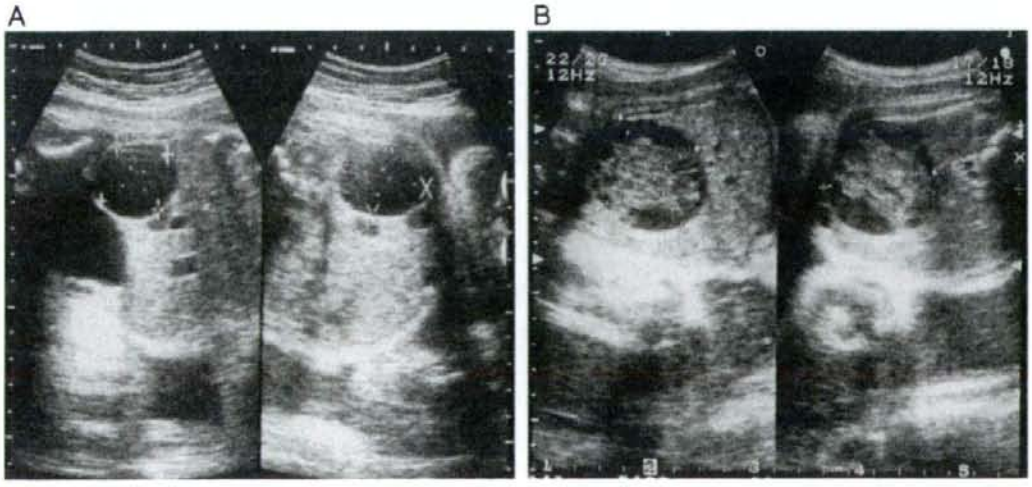

Figure 1 Fetal cystic tumors identified by ultrasonography in the third trimester. (A) A representative example of a simple cyst. The cyst was completely anechoic. Note the surrounding thin wall. (B) A representative example of an echogenic complex cyst.

Table 1 Perinatal appearances of fetal ovarian cysts in relation to prenatal ultrasound pattern and size

Case	1st prenatal scan	Size at prenatal diagnosis (mm)	Last prenatal scan	Maximum diameter (mm)	Outcome in pregnancy	Postnatal outcome	Pathology
1	S	45	S	45	Reduced	S.R.	
2	S	48	S	48	Reduced	S.R.	
3	S	75	S	75	Reduced	Surgery	Simple cyst
4	S	32	S	32	Reduced	S.R.	
5	S	31	S	34	S.R.	–	
6	S	23	S	23	S.R.	–	
7	S	41	S	41	Reduced	S.R.	
8	S	44	S	66	Increased	S.R.	
9	S	50	C	56	No change	Surgery	Simple cyst with necrosis, calcification and torsion
10	S	40	C	41	No change	Surgery	Simple cyst with calcification and hemorrhage
11	S	49	C	49	No change	Surgery	Simple cyst with hemorrhage
12	C	32	C	32	No change	Surgery	Simple cyst with torsion and adhesion between bowel and ovarian cyst
13	C	42	C	46	No change	Surgery	Simple cyst with necrosis, calcification and torsion
14	C	46	C	51	No change	Surgery	Simple cysts with calcification and hemorrhage
15	C	40	C	40	No change	S.R.	
16	C	55	C	55	Reduced	S.R.	

S = Simple cyst; C = complex cyst; S.R. = Spontaneous resolution.

6 months after birth (Table 1). What happened to the ovary after the cyst resolved remains unknown, because we did not perform the second look observation by laparoscopy.

With regard to the five complex cysts, four of them showed no change in size during prenatal ultrasound monitoring. Postnatally, three (75%) of 4 infants underwent surgery for persistence of the cyst or postnatal evidence of torsion or evidence of neoplastic changes (Table 1, Patients 12, 13 and 14). Histopathological examination showed two simple cysts with torsion and one simple cyst with intracystic hemorrhage. The other two complex cysts disappeared on follow-up imaging within 11 months after birth as confirmed by follow-up ultrasonography or other imaging. We don't know whether the ovary after the cyst resolved leaved a normal ovary or disappeared on follow-up imaging because the laparoscopic second look observation was not performed in all infants.

Surgery was performed for excision of 7 of 16 cysts. The procedure included oophorectomy, sometimes with enucleation. Oophorectomy was performed to the cases that were detected the ischemic necrosis and self-amputation of the fetal ovarian cyst. Microscopic examination indicated that all seven cysts were simple cysts (Table 1). Three out of the seven cysts were simple cysts with torsion, but adhesion between the bowel and ovary was noted in one case during surgery. The other three cysts showed intracystic hemorrhage and one cyst was simple cyst without specific epithelial findings. The histopathological finding was benign and neoplastic tumor was not detected in our study. But Pietro Bagolan et al. recommended the surgery of the ovarian cysts with an ultrasound pattern of torsion which persisting after birth [8]. We also think that fetal ovarian complex cysts should be managed carefully after birth because 3 of 6 complex cysts that surgeries were performed were cysts with torsion and 1 of 3 cysts with torsion showed the adhesion between the bowel and the cyst.

The mean maximum diameter of the ovarian cysts before delivery that were subsequently excised surgically at postnatal period (50 ± 13.4 mm) was not different from that of ovarian cysts that resolved spontaneously (42.8 ± 12.8 mm, $P = 0.2918$).

4. Discussion

The majority of fetal ovarian cysts are considered to result from excessive hormonal stimulation [10,11] and resolve spontaneously after birth and that they are of no clinical significance. The detection of ovarian cysts in utero has increased lately, with the increased use of routine ultrasonography, raising questions on the perinatal management of these anomalies. After the diagnosis of fetal ovarian cyst, serial ultrasound examinations are necessary in order to detect any torsion. It has been suggested that such complication depends on the size of the fetal ovarian cyst [6]. However, there was no such correlation in our series, as we did not detect any difference in the mean size of cysts with and without torsion at diagnosis. The mean maximum diameter of ovarian cysts with torsion was 44.6 ± 12.1 mm, while that without torsion was 44.2 ± 12.8 mm.

Interestingly, 7 of the 11 simple cysts (63.6%) disappeared spontaneously during pregnancy or within 2 months after birth. The rate of spontaneous resolution of simple cysts was higher than that of complex cysts (40.0%).

Surgery was performed for excision of seven cysts. Indications for surgeries in our hospital were the following: 1) large fetal ovarian cysts that did not diminish in size at postnatal scan, 2) complex cysts that showed evidence of torsion at postnatal scan, and 3) cysts suspected to be neoplastic tumor. In our experience, cyst size did not predict the risk of ovarian loss; the mean of maximum prenatal diameter of ovarian cysts that were subsequently excised surgically was not different from that of cysts that resolved spontaneously.

We did not carry out any ovarian cyst aspiration during fetal and neonatal life during the study period. Although aspiration of large simple cysts might prevent serious complications, we didn't aspirate them because we took into consideration the possibility of fetal malignant ovarian tumor. And the selection of cases to undergo aspiration is difficult because 7 of the 11 simple cysts (63.6%) disappeared spontaneously during pregnancy or within 2 months after birth. After the diagnosis of fetal ovarian cyst is established, we recommend a conservative approach that includes serial ultrasound examinations and follow the course of the anomaly until spontaneous resolution.

Complex cysts should be managed carefully because they may represent entities such as intestinal duplications or tumors. Fetal cystadenomas and granulosa cell tumors have been reported in the literature [14,15]. It is possible that intracyst hemorrhage could result in fetal anemia or torsion of the cyst could cause bowel obstruction [8,12,13].

In our study, two out of eight complex cysts resolved spontaneously. A cyst with an echo pattern of torsion that disappears spontaneously is clinically important, but knowledge of the real nature of such cyst is difficult. Gohar et al, in their report of the case of spontaneously disappearing cyst, suggested that it could be represented by a cyst that underwent initial torsion and subsequent spontaneous detorsion [16]. What happened to the ovary after the cyst resolved remains unknown, because we did not perform the second look observation by laparoscopy, but we also think that there is a possibility of the spontaneous detorsion of the fetal ovarian tumor. Pietro Bagolan et al. reported the case that spontaneously disappeared at ultrasound, and said the possibility of the self-amputation of the ovary and adhesion to other organs [8].

Furthermore, laparoscopic surgery was performed to remove four out of seven fetal ovarian cysts. Since the number of cases in this report was small, it is difficult to determine the conditions that dictate a requirement for, and a timing of any surgical intervention. However, from the point of view of minimally invasive management, laparoscopic exploration or conservative management may be necessary as the first line intervention in terms of diagnosis and therapy of the fetal ovarian cysts.

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Giant cystic meconium peritonitis associated with a cloacal anomaly: case report

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Cloacal anomaly;
Giant cystic meconium peritonitis;
Hydrocolpos

Abstract This report describes a case of giant cystic meconium peritonitis (GCMP) associated with a cloacal anomaly. Antenatal ultrasonography and magnetic resonance imaging demonstrated persistent fetal ascites, bilateral hydronephrosis, and 3 pelvic cystic structures. The baby girl showed duplicated hydrocolpos and a single orifice of the cloaca with a long common channel inducing a urinary outflow obstruction. After constructing a diversion colostomy, a cutaneous vesicostomy was necessary to prevent recurrent urinary tract infections. These findings are consistent with a prenatal diagnosis of cloacal anomalies, thus suggesting an association with severe obstruction of lower urinary tract and meconium peritonitis.Most of reported cases of meconium peritonitis associated with the cloaca show fibroadhesive types with scattered intraperitoneal calcifications and adhesions. However, the present case showed a rare GCMP suggesting continuous urinary influx via the fallopian tubes until the later stage of intrauterine life.

Meconium peritonitis (MP) is aseptic peritonitis occurring because of a spill of meconium in the abdominal cavity through one or several intestinal perforations, which has taken place during intrauterine life [1]. Commonly, MP is complicated with an intestinal obstruction, such as intestinal atresia and meconium ileus. Several pediatric surgeons have described patients with a cloacal anomaly showing intraperitoneal calcification or a dense plastic peritonitis associated with hydrometrocolpos or hydrosalpinx [2-6].

This report documents a case of giant cystic meconium peritonitis (GCMP) associated with a cloacal anomaly. To the

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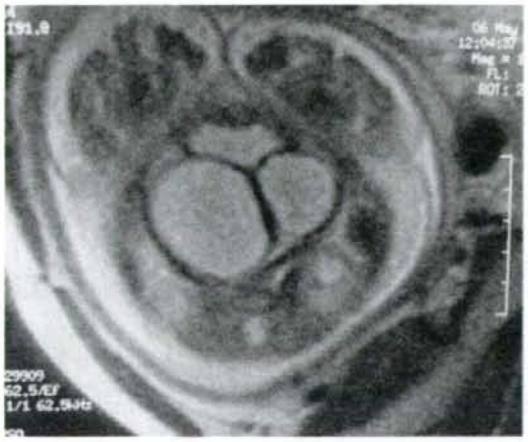

Fig. 1 Demonstration of duplicated hydrocolpos behind the bladder on magnetic resonance imaging.

best of our knowledge, there are no similar reports showing GCMP associated with cloacal malformations. The pathophysiology of this rare condition is herein discussed.

1. Case report

A 32-year-old female, gravida 0 para 0, was referred to the Department of Obstetrics and Gynecology of our University Hospital (Nagasaki University Hospital, Nagasaki, Japan) at 31 5/7 weeks of gestation for evaluation of fetal ascites. A fetal ultrasound examination and magnetic resonance imaging showed fetal ascites, bilateral hydronephrosis, and 3 abdominal cystic masses (Fig. 1). At 33 6/7 weeks of gestation, a cesarean delivery was performed because of an apparent decrease in the amnion and nonreassuring fetal heart rate pattern. The neonate weighing 2506 g and Apgar scores of 5 and 6 after 1 and 5 minutes, respectively, was delivered. A physical examination revealed generalized edema, abdominal distension, ambiguous genitalia, and anal atresia with a single perineal opening. By applying contrast medium during cystoscopy, the bladder and duplicated hydrocolpos were revealed. Despite of the passage of urine, distension of upper abdomen persisted. A laparotomy revealed a large cystic mass occupying the upper abdomen, which was incised and viscous fluid was drained. The bowel could be seen through the posterior wall of the cyst and was exposed after an incision. Multiple adhesions were present in the peritoneal cavity, but there was no evidence of perforation of the bowel. A transverse colostomy was performed for fecal diversion, and a drain was inserted into the cyst. The postoperative course was uneventful, and there was no discharge from the drain. Histologically, the contents of the cyst consisted of amorphous eosinophilic material, containing inflammatory cells such as neutrophils, eosinophils, macrophages, and lymphocytes as well as a small number of erythrocytes. Intestinal epithelial cells were not evident. Genitography showed dilated duplicated hydrocolpos, bladder, and rectum communicating with long, narrow common channel. There was no spillage of contrast medium into the peritoneal cavity (Fig. 2). The patient underwent a cutaneous vesicostomy for a recurrent urinary tract infection 4 months after birth. Further reconstructive surgery for the cloacal malformation and imperforate anus is planned to be attempted at a later date.

2. Discussion

In the present case, the operative findings indicated giant cystic type of MP; nevertheless, there was no evidence of bowel perforation and obstruction. Lorimer and Ellis [7] described 3 major types of MP—fibroadhesive, generalized, and cystic. Among the cystic type, GCMP is relatively unusual. The entire peritoneal cavity is converted into a large meconium-filled cyst lined by a thick membrane containing

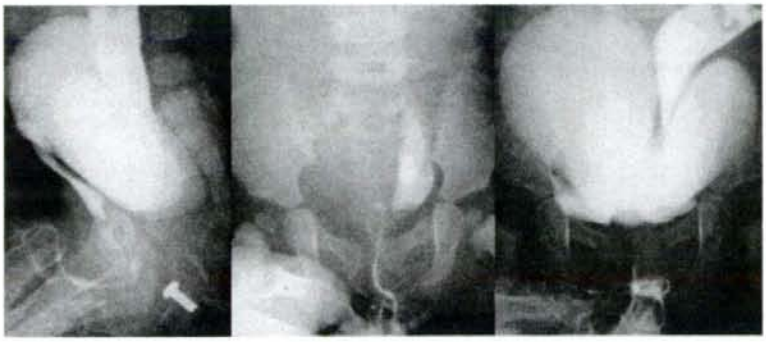

Fig. 2 Genitography demonstrated duplicated hydrocolpos behind the bladder and rectum as a narrow fistula. The level of confluence was observed between the pubococcygeal line and the midline. The common channel was narrow and it measured 3.5 cm in length. The distance from the bladder neck to confluence was 1.6 cm. Spillage of contrast media into the peritoneal cavity was not observed.

multiple calcium deposits and plaques, and the intestine are collapsed and compressed against the posterior abdominal wall [8].

A *cloacal anomaly* is defined as the junction of the rectum, vagina, and urethra into a single common channel [9], which is because of an earlier embryonic arrest during development in a female neonate [10]. In the presence of the lower urinary tract obstruction, urine might drain from the fetal bladder into the vagina and rectum, and the mixture of urine and meconium can occur. Regarding MP associated with cloacal anomaly, most authors have speculated that the route of the urine and meconium leakage is via the fallopian tubes. As urine accumulates in the vagina, a large hydrocolpos could develop. Urine containing a meconium component escapes from hydrocolpos via the fallopian tubes into the peritoneal cavity and causes intrauterine peritonitis [4,5,11-14]. In a rare case, Stephenson et al [3] reported a case of MP associated with cloacal malformation and perforated hydrocolpos.

The pathophysiology of hydrocolpos in this case is thought to be secondary to a disturbance of urinary efflux and reflux into the vagina probably because of a long and narrow cloacal channel. Prenatal continuous urinary back-flow into the vagina may increase intravaginal pressure resulting in a hydrocolpos. The route for an influx of meconium into the peritoneal cavity might have occurred via regurgitation through the fallopian tubes, or a perforation of hydrocolpos or bowel may also have been possible. Of these 2 hypotheses, the former might be more likely in this case because neither a perforation of hydrocolpos nor the bowel was observed. In addition, the intrauterine healing of a perforated hydrocolpos or bowel may also be possible.

In the present case, the type of MP was quite unusual; most of reported cases of MP associated with cloacal anomaly generally display fibroadhesive type [2,3,11,15]. Petrikovsky et al [16] suggested that urine enters the abdominal cavity via the fallopian tubes at an early stage, causing "transient" fetal ascites, however, chronic urinary and meconium irritation of the tubal mucosa may cause tubal obstruction, which may lead to the subsequent development of hydrocolpos and the compression of the ureters and bladder, which leads to hydronephrosis at a later stage. Transient fetal ascites in a cloacal anomaly may indicate the formation of a fibroadhesive type of MP. In the present case, however, it appeared that the peritoneal cavity developed adhesion because of the initial inflow of urine mixed with meconium, and the subsequent continuous influx and a late obstruction of fallopian tubes because of inflammation might thus have led to the formation of a giant pseudocyst.

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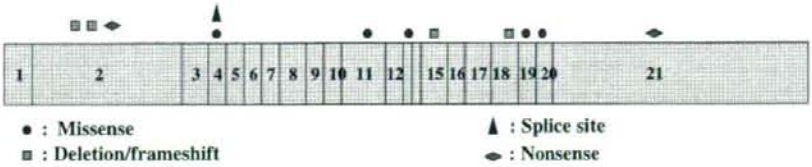

Fig. 1 Distribution of new mutations on the *ATP7B* gene

with WD, ten out of 19 of the novel mutations found were localized on exons 14, 16, and 19, which belong to the group of exons previously found to be the site of many frequent, as well as rare, WD-causing mutations. The genetic analysis of 56 Saudi patients with WD revealed that 50% of them had mutations in three exons (8, 19, and 21) of the *ATP7B* gene. Mutations in exon 19 and 21 were unique for Saudi patients (Takeshita et al. 2002). A novel deletion mutation, c.4193delC, in exon 21 of the *ATP7B* gene mutation, appears to be unique to Saudi patients and is found frequently in this ethnic group (Al Jumah et al. 2004; Majumdar et al. 2000, 2003). This is in contrast to our study, in which the novel mutations detected were randomly distributed all over the *ATP7B* gene, including exons (2, 4, 5, 7, 11, 13, 15, 17–21; Fig. 1).

Again, the majority of mutations detected in this study were found in the homozygous state (42 patients from 26 independent families), whereas in the study of Loudianos et al. (1999), most mutations detected were in the compound heterozygous state, and in only four cases, homozygosity was present. This may be explained by the high percentage of consanguinity in our study (75%) compared with consanguinity in the Egyptian population (32–35%).

Although homozygous mutations were found in 42 patients from 26 independent families, six of those patients from six different families were the result of nonconsanguineous mating. Also heterozygous mutations were found in six patients, two were the result of consanguineous mating. This unexpected finding, together with the finding of one patient homozygous for both p.N1270S and p.T1434M mutations, necessitates a larger-scale population study for the carrier frequency and the origins of these mutations in different families in this community.

Conclusion

The mutational spectrum of *ATP7B* among Egyptian children presenting with WD is very heterogenous, which mandates a larger-scale population screening to identify the carrier rate in this community. Frameshift and nonsense mutations may result in earlier presentation of the disease at childhood. Despite mutation heterogeneity in Egyptian patients, genotype–phenotype correlation analysis seems to be promising in this population, as many patients carry homozygous mutations.

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ORIGINAL ARTICLE

Does increased nuchal translucency indicate a fetal abnormality? A retrospective study to clarify the clinical significance of nuchal translucency in Japan

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Abstract The results of a chromosomal test by genetic amniocentesis in 58 cases with an increased nuchal translucency (NT; ≥3 mm thickness) revealed 47 cases showing a normal karyotype (81%) and 11 cases (19%) showing an abnormal karyotype. However, the cases of a normal karyotype with increased NT also included those with fetal abnormalities. Among the 49 cases in which NT was observed during the first trimester and then subsequently disappeared, chromosomal abnormalities were observed in five, and fetal abnormalities other than chromosomal abnormalities were observed in two. Meanwhile, all nine cases in which an increased NT remained or in which NT continued to increase in size during the second trimester were diagnosed as having cystic hygroma, and chromosomal abnormalities were found in six cases (67%). It should be noted that the shape of increased NT includes NT with a notch (notched NT) and NT without a notch (smooth NT). Among the 20 cases of notched NT, chromosomal abnormalities were observed in eight (40%), and cystic hygroma was observed in nine (45%). On the other hand, among the 38 cases of smooth NT, chromosomal abnormalities were observed in three (7.9%), but no cystic hygroma was observed. Our results confirm that increased NT does not always indicate a fetal abnormality. Whether NT thickness should be measured as a screening tool for fetal abnormalities remains controversial. However, increased NT may be detected by chance, because a maternal–fetal medical examination using ultrasonography is usually performed in Japan. It is therefore considered to be extremely important to establish a system in which cases are referred to obstetricians who are licensed clinical genetic specialists to obtain appropriate genetic counseling whenever increased NT is clinically observed.

Keywords Nuchal translucency · Prenatal diagnosis · Genetic counseling · Ultrasonography · Obstetrics · Genetic amniocentesis · Screening marker

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Introduction

Nuchal translucency (NT) is a low-intensity area observed in the fetal posterior cervical region upon ultrasonography at 11–14 weeks of gestation. NT itself is a finding inherent in all fetuses and is not necessarily an abnormal finding. The relationship between increased NT and chromosomal abnormalities was first reported by Nicolaides et al. (1992). Since then, the relationship with diseases other than chromosomal abnormalities, such as cardiac, genetic, and urinary system diseases has been described in various reports (Nicolaides et al. 1992; Souka et al. 2005; Westin et al. 2006). However, although there are many reports on the usefulness of NT measurement as a marker for chromosomal abnormalities, maternal age and the degree of increased NT vary in the medical literature, and the frequency of chromosomal abnormalities in cases of increased NT ranges from 11% to 88%, which also indicates differences. Therefore, no consistent viewpoint has emerged (Pandya et al. 1995; Brambati et al. 1995; Szabo et al. 1995).

It is known that even when increased NT is observed in the first trimester, in most cases, it later spontaneously

disappears. However, even in cases in which it disappears, the frequency of observing chromosomal abnormalities and other fetal abnormalities has been reported to be higher than that in the general population (Müller et al. 2004). In addition, there are cases in which the increased NT observed during the first trimester lso remains into the second trimester, and it is then diagnosed as cystic hygroma. However, it is difficult to diagnose this abnormality as cystic hygroma during the first trimester.

In Europe and the United States, a One-Stop Clinic for the Assessment of Risk (OSCAR) has been implemented, and a screening test according to maternal age with a serum marker for Down syndrome in addition to NT is conducted. In addition, NT measurement has is one of the items of the screening test for Down syndrome (Bindra et al. 2002).

On the other hand, the situation in Japan is that ultrasonography is almost universally used as part of the normal maternal health checkup. Therefore, whereas the correlation between increased NT and chromosomal abnormalities has been reported in Europe and the United States, NT measurement became widely used in Japan without sufficient understanding of the clinical significance of such measurement and how to accurately interpret such findings. It is therefore common for increased NT to be identified by chance during ultrasonographic examinations, and a serious issue has recently arisen in which artificial abortion often tends to be selected when increased NT is observed in a fetus, because sufficient genetic counseling has not been conducted.

Therefore, to clarify the clinical significance of NT in Japan, we studied the frequency of chromosomal abnormalities in cases of increased NT, the frequency of fetal abnormalities in cases of a normal karyotype with increased NT, the frequency of fetal abnormalities in cases with disappearance of NT, and the relationship between NT shape and fetal abnormalities.

Materials and methods

Subject

To obtain data of chromosomal karyotype, we included 171 pregnant women who received genetic amniocentesis at 16 weeks of gestation between February 1998 and May 2007 at the Department of Obstetrics and Gynecology at Nagasaki University Hospital. This included 102 cases with advanced maternal age (≥35 years old), 58 with NT thickness of at least 3 mm (increased NT), five with a history of delivering children with chromosomal abnormalities, and six others (four of a request for a chromosomal test, one with a history of delivery with Noonan syndrome, and one with a history of delivering a child with a cardiac abnormality). All cases were managed at regional private clinics and referred to Nagasaki University Hospital for genetic counseling. For all cases, genetic counseling was performed by obstetricians who were licensed clinical genetic specialists. Patient consent before measuring NT was obtained, and NT thickness was measured between 11 and 14 weeks of gestation in 171 cases of single pregnancy.

NT measurement by ultrasonography

NT was measured by an ultrasound specialist according to the method stipulated by the Fetal Medicine Foundation (Nicolaides et al. 1999). NT thickness of ≥3 mm was defined as increased NT, because the frequency of abnormal karyotypes in fetuses with NT thickness ≥3 mm at 11–14 weeks of gestation was higher than the respective number expected on the basis of maternal age (Pandya et al. 1995). Once fetuses with increased NT were detected at 11–14 weeks of gestation, they were followed as cases of increased NT until the end of pregnancy. We measured NT thickness before genetic amniocentesis at 16 weeks of gestation. We also performed a fetal screening of structural abnormalities by ultrasonography at 20 weeks of gestation. When increased NT at 11–14 weeks of gestation was not detected visually or had decreased to <3 mm at 16 weeks of gestation, those cases were defined as cases of NT disappearance.

Classification of the shape of increased NT

Cases in which NT had a smooth surface were defined and classified as smooth NT (s-NT group; Fig. 1a), and those in which the NT surface had a notch-like dent were classified as notched NT (n-NT group; Fig. 1b). The frequency of chromosomal abnormalities and the frequency of cases diagnosed as cystic hygroma in the second trimester were compared between the groups.

Statistical analysis

For statistical analysis, the Mann–Whitney U test was used. A value of $P < 0.05$ was determined to indicate a significant difference.

Results

Frequency of fetal chromosomal abnormalities in fetuses with increased NT

As a result of genetic counseling at our hospital, among the 171 cases in which subjects had undergone genetic

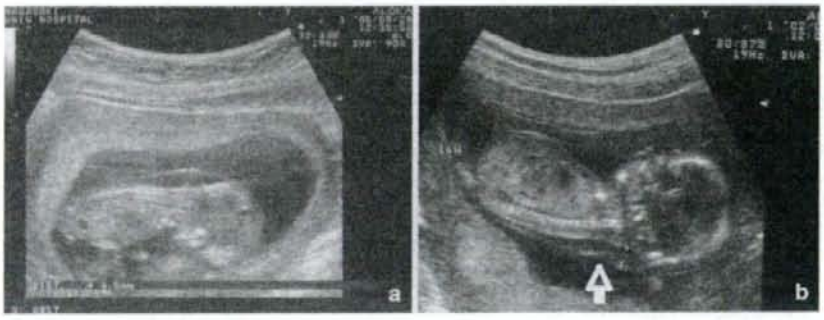

Fig. 1 Classification according to the shape of nuchal translucency (NT). **a** NT with a smooth surface was classified as smooth NT, and **b** NT with a notch (*arrow*) was classified as notched NT

amniocentesis, an increased NT was observed in 58 cases. Among the 58 cases with increased NT, chromosomal abnormalities were observed in 11(19%), including five of trisomy 21, for of trisomy 18, one of monosomy X, and one of mosaic (Fig. 2).

Frequency of chromosomal abnormalities in fetuses demonstrating NT measuring less than 3 mm

The relationship between increased NT and chromosomal abnormalities has been reported, but some cases without an increased NT also have chromosomal abnormalities. Therefore, the frequency of fetal abnormalities was studied in 113 cases with an NT thickness <3 mm. Indications for undergoing a chromosomal test were advanced maternal age in 102 cases, history of delivery with chromosomal abnormalities in five, history of delivery with Noonan syndrome in one, history of delivering a child with a cardiac abnormality in one, and request for a chromosomal test in four. Among these 113 cases, chromosomal abnormalities were observed in six (5%), including four of trisomy 21 and two of trisomy 18. One case of single atrium and single ventricle (1/107 cases; 0.9%) was detected in 107 fetuses with normal karyotype and normal NT.

Abnormalities in fetuses with normal karyotype and increased NT

As various fetal abnormalities other than chromosomal abnormalities have been reported for cases with increased NT, we studied which of the possible causes of increased NT were present. The screening of structural abnormalities by ultrasonography was performed at 20 weeks gestation. As a result of the amniotic fluid chromosomal test, among the 58 cases with NT measuring at least 3 mm, 47 (81%) demonstrated normal karyotype. Among the 47 normal karyotype cases with NT measuring at least 3 mm, fetal abnormalities were observed in five (5/47 cases; 10.6%), including one of cardiac abnormality, two of fetal hydrops, one of fetal pleural effusion, and one of diaphragmatic hernia (Fig. 2).

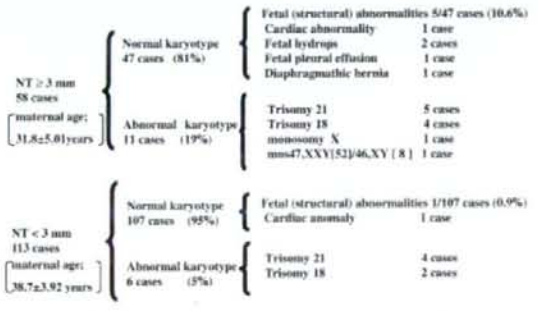

Fig. 2 Nuchal translucency (NT) thickness, fetal chromosomal abnormalities, and fetal structural abnormalities. A flow chart of 58 cases with an increased NT of at least 3 mm observed in the first trimester and the 113 cases with an NT measuring less than 3 mm

Outcomes in the cases of increased NT that later disappeared

It is known that most cases of increased NT observed in the first trimester disappear as pregnancy progresses. We therefore investigated the frequency of fetal abnormalities in such cases. The average NT thickness in cases of increased NT that later disappeared was 4.1 ± 1.4 (mm). Among the 58 cases in which increased NT was observed in the first trimester, 49 (84%) showed a disappearance of NT in the second trimester. In five of those cases, chromosomal abnormalities (three of trisomy 21 and two of trisomy 18) were observed; and in another two, congenital abnormalities (one each of diaphragmatic hernia and single atrium and single ventricle) were observed (Fig. 3).

Subsequent outcomes in cases of increased NT that did not later disappear

Meanwhile, among the 58 cases in which NT was observed in the first trimester, nine (16%) did not show NT disappearance, even during the second trimester. All of these cases were diagnosed to have cystic hygroma, and chromosomal abnormalities were observed in six (67%) of the nine cases. The breakdown includes two cases of trisomy

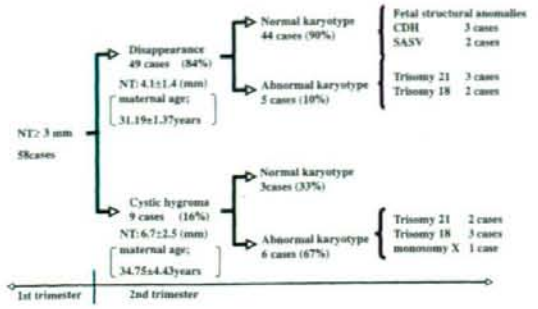

Fig. 3 Outcome of nuchal translucency (NT) observed in the first trimester. The outcomes of 58 cases with increased NT measuring at least a 3 mm in the first trimester are shown in the flow chart. In the second trimester, increased NT disappeared in 49 cases (84%) but remained in nine (16%) who were later diagnosed to have cystic hygroma. *CDH* congenital diaphragmatic hernia, *SASV* single atrium and single ventricle

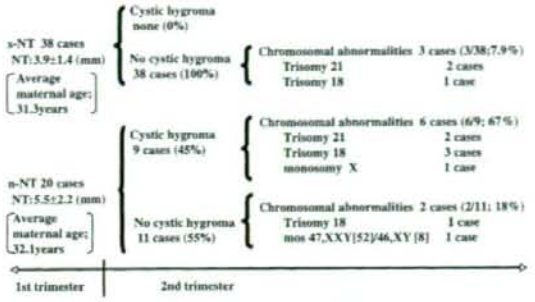

Fig. 4 Relationship between nuchal translucency (NT) patterns and fetal abnormalities. The smooth NT (s-NT) group consisted of 38 cases, whereas the notched NT (n-NT) group consisted of 20 cases. In the s-NT group, three cases (7.9%) had chromosomal abnormalities. In the n-NT group, eight cases (40%) had chromosomal abnormalities. The frequency of chromosomal abnormalities in the n-NT group was significantly higher than that in the s-NT group ($P = 0.0027$)

21, three of trisomy 18, and one of monosomy X (Fig. 3). The average NT thickness in the nine cases of cystic hygroma was 6.7 ± 2.5 (mm).

Relationship between NT shape and fetal abnormalities

The average NT thickness in 38 cases of s-NT was 3.9 ± 1.4 (mm), whereas that in 20 cases of n-NT was 5.5 ± 2.2 (mm). There was significant difference between the groups ($P < 0.0006$). All nine cases diagnosed as cystic hygroma colli in the second trimester demonstrated increased NT with a notch in the first trimester. Maymon et al. (2001) reported a notch in 62% of NT cases that showed increased NT in the first trimester and that were later diagnosed with Down syndrome. It was thus indicated that NT with a notch is a marker more closely related to Down syndrome. As described above, because cystic hygroma has a high frequency of being accompanied by chromosomal abnormalities, we analyzed the relationship between NT with a notch observed in the first trimester and chromosomal abnormalities as well as cystic hygroma, and we studied whether NT with a notch observed in the first trimester can be regarded as a marker for fetal abnormalities and cystic hygroma.

As a result of classifying 58 cases of increased NT according to the presence or absence of a notch, the s-NT group consisted of 38 cases, whereas the n-NT group consisted of 20 cases (Fig. 4). In the s-NT group, three cases had chromosomal abnormalities (7.9%; two of trisomy 21, one of trisomy 18), and in the n-NT group, eight (40%) had chromosomal abnormalities. The frequency of chromosomal abnormalities in the n-NT group was significantly higher than that in the s-NT group ($P = 0.0027$). Among the eight cases in the n-NT group with chromosomal abnormalities indicated, six were diagnosed to have cystic hygroma in the second trimester, with two of trisomy 21, three of trisomy 18, and one of monosomy X. The remaining two were diagnosed as one case each of mosaic (mos 47,XXY[52]/46,XY[8]) and 18 trisomy. In addition, nine cases of cystic hygroma in the second trimester were classified as belonging to the n-NT group, but none were classified as belonging to the s-NT group ($P = 0.0001$).

Discussion

Among the 58 cases with increased NT, 11 (19%) had chromosomal abnormalities. The frequencies of chromosomal abnormalities in cases with increased NT varies in reports by different authors, but it was 19.2% and 16.2%, respectively, in one study of 11,315 cases (Kagan et al. 2006) and one of 1,015 cases (Pandya et al. 1995), and our study results were also similar. Indeed, the frequency of accompanying chromosomal abnormalities is high in cases with increased NT, but conversely, 81% of the cases with increased NT demonstrate a normal karyotype. This means that most cases are normal karyotype fetuses despite increased NT. The presence or absence of chromosomal abnormalities cannot be determined according to NT thickness, as performing NT measurements is only a screening test. It is therefore necessary to be aware that a chromosomal test is also required to verify a diagnosis of chromosomal abnormalities.

Among 113 cases with NT measuring <3 mm, chromosomal abnormalities were observed in six (5%). As the 113 cases included 102 cases (90%) of mothers with advanced maternal age (i.e., >35 years of age) and all six cases with chromosomal abnormalities were included in such advanced maternal-age cases, it is believed that chromosomal abnormalities cannot be ruled out, even if NT

thickness was <3 mm. Also, the frequency of chromosomal abnormalities is also more significantly affected by maternal age than by increased NT.

As for the outcome of the 47 cases that had increased NT but demonstrated a normal karyotype, fetal abnormalities were observed in five cases (11%). The breakdown includes two cases of fetal hydrops and one each of cardiac disease, fetal pleural effusion, and diaphragmatic hernia. The reported causes of increased NT include chromosomal abnormalities, heart failure due to cardiovascular and great-vessel anomalies, diaphragmatic hernia, venostasis in the head and neck, abnormal development and outflow obstruction of the lymph system, renal and urinary system, nervous system, genetic disease, and such. Various causes were observed in our study as well. As most instances of NT disappear during the second trimester despite having previously been observed, NT is a thus considered to be a transient physiological finding of the skin during the first trimester, and because it cannot be explained by any single mechanism, it should therefore be used as a collective term in transient findings. Therefore, regarding outcome after detection of NT, NT disappears during the second trimester of pregnancy in some cases but continues to grow in others.

We studied the outcome of 49 cases in which increased NT was observed in the first trimester and disappeared during the second trimester. Among these cases, chromosomal abnormalities (three of trisomy 21 and two of trisomy 18) were observed in five cases, and congenital abnormalities (one case each of diaphragmatic hernia, single atrium, and single ventricle) were observed in two cases. These results indicate that it is not a finding that rules out disease, even when a previously observed increased NT has disappeared, and it is therefore necessary to carefully follow-up such with an increased NT.

The relationship between cystic hygroma and chromosomal abnormalities has been reported, but it is difficult to differentiate NT from cystic hygroma in the first trimester. In addition, no consensus diagnostic criteria have been established for cystic hygroma in the first trimester. It is relatively easy to diagnose so-called multilocular septated cystic hygroma that has septal walls in the fetal posterior cervical region. However, it is very difficult to differentiate nonseptated cystic hygroma without septal walls and an increased NT (Pistorius and Page-Christiaens 2005). In our study, the frequency of chromosomal abnormalities in the n-NT group was significantly higher than that in the s-NT group ($P = 0.0027$). In addition, the nine cases subsequently diagnosed to have cystic hygroma were classified as n-NT, and none were classified as s-NT ($P = 0.0001$). A relationship between n-NT and Down syndrome has been indicated (Maymon et al. 2001), and the cases with cystic hygroma had a high frequency of chromosomal abnormalities (67%) in our study, suggesting a positive relationship between. The increased NT observed in the first trimester includes the initial findings of cystic hygroma in the second trimester, and it was indicated that such cases tend to have a notch in NT. The average NT thickness in nine cases of cystic hygroma was significantly increased compared with that in cases of increased NT that later disappeared (6.7 ± 2.5 mm vs. 4.1 ± 1.7 mm, respectively; $P = 0.002$). There was also significant difference in NT thickness between the s-NT group and the n-NT group ($P < 0.0006$). Further large-scale studies will clarify the association between NT thickness in the first trimester and disappearance of increased NT in the second trimester or cystic hygroma in the second trimester. The association between fetal abnormalities and NT disappearance or shape in fetuses with normal karyotype is interesting, though the sample numbers in the our study were too small to give sufficient strength to the analysis. Further study regarding this association should be performed.

In Europe and the United States, a screening system for chromosomal abnormalities has been established that integrates and determines maternal age, and maternal serum-marker tests results in addition to NT measurements while calculating the probability of Down syndrome. NT measurements are handled in a similar way as other maternal serum markers. Therefore, clinical fetal chromosomal abnormalities and fetal structural abnormalities are never evaluated by NT measurements alone.

Conversely, in Japan, maternal serum markers were introduced as a screening test for Down syndrome in the early 1990s, and it became widely used because of its simplicity without fully understanding that this test is only a screening test. Because a system of genetic counseling had at that time not been developed, the explanation of the test results was therefore insufficient, and a situation occurred in which couples sometimes elect to have an artificial abortion before undergoing genetic amniocentesis, which would verify such a diagnosis. Therefore, a negative opinion of the implementation of maternal serum markers was issued by the Health Sciences Council in 1999 in Japan.

In addition, regarding NT measurement, a similar problem to that of maternal serum markers has recently been identified. In Japan, NT can be easily measured because fetal ultrasonography is normally performed as part of the regular maternal health checkup. Therefore, these measurements alone became widely used before the clinical significance of NT measurement was fully understood. As a result, we are now struggling with the interpretation and explanation of NT in Japan. In addition, because NT can be observed in images and is indicated as a numeric value, the anxiety that parents feel may be greater than that for the results of serum markers. Parents of a fetus

with an increased NT may elect to have an artificial abortion without pursuing a confirmation of diagnosis via amniotic fluid testing before sufficiently understanding the significance of NT.

In conclusion, our results confirmed that increased NT does not always indicate a fetal abnormality. As NT measurement is only a screening test and not verification of any diagnosis, normal fetuses with increased NT should not be artificially aborted. Genetic counseling including information regarding both NT and genetic amniocentesis should be performed in all cases before and after measuring NT. Whether NT thickness should be measured as screening of fetal abnormalities remains controversial in Japan. However, increased NT may be detected by chance, because a maternal–fetal medical examination using ultrasonography is usually performed in Japan. It is therefore considered to be extremely important to establish a system in which all cases of increased NT are referred to obstetricians who are licensed clinical genetic specialists to obtain appropriate genetic counseling regarding NT.

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ORIGINAL ARTICLE

Association of genetic variations of genes encoding thrombospondin, type 1, domain-containing 4 and 7A with low bone mineral density in Japanese women with osteoporosis

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Abstract Twins and family studies have shown that genetic factors are important determinants of bone mass. Important aspects of bone mineral density (BMD) regulation are endocrine systems, notably hormonal regulation of adrenal corticoids, as indicated by clinical knowledge of glucocorticoid-induced osteoporosis. Glucocorticoid is known to negatively regulate bone mass in vivo, and glucocorticoid increases thrombospondin messenger ribonucleic acid (mRNA) levels. We studied single nucleotide polymorphisms (SNPs) in genes encoding thrombospondin, type 1, domain-containing 4 and 7A (THSD4 and THSD7A) for possible association with lumbar and femoral BMD among 337 Japanese women with osteoporosis who participated in the BioBank Japan project. Genetic variations of THSD4 and THSD7A loci displayed significant association with lumbar and femoral BMD. Most significant correlation was observed for THSD7A SNP rs12673692 with lumbar BMD ($P = 0.00017$). Homozygous carriers of the major (G) allele had the highest BMD [0.886 ± 0.011 g/cm^2, mean $\pm$ standard deviation (SD)], whereas heterozygous carriers were intermediate (0.872 ± 0.013 g/cm^2) and homozygous A-allele carriers had the lowest (0.753 ± 0.023 g/cm^2). THSD4 SNP rs10851839 also displayed strong association with lumbar BMD ($P = 0.0092$). In addition, both THSD7A and THSD4 displayed significant association with femoral BMD in a recessive model ($P = 0.036$ and $P = 0.0046$, respectively). Results suggest that variations of THSD7A and THSD4 loci may be important determinants of osteoporosis in Japanese women.

Keywords Association study · Bone mineral density · Single nucleotide polymorphism · THSD4 · THSD7A

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Introduction

Osteoporosis, one of the most prevalent disease conditions in the elderly, is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture (National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy 2001). The disease is diagnosed by low bone mineral density (BMD) and the presence of fragility fractures (Orimo et al. 2001). As with many other common diseases, in this disease, multiple factors including genetic variations determine predisposition for the onset or progression of osteoporosis, as indicated by genetic–epidemiological studies (Peacock et al. 2002; Albagha and Ralston 2003). Numerous studies on genetic risks for osteoporosis have been investigated to date, mainly by association studies

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Correlation Between Preeclampsia and Prevalence of Polymorphism of Angiotensinogen, Methyleneteterahydrofolate Reductase and Factor V, Prothrombin Genes Among Japanese Women

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OBJJECTIVE: To determine the genotypes of four candidate genes in Japanese women with a history of preeclampsia, and in a control group of parous woman.

STUDY DESIGN: Fifty-two pregnant women with a history of preeclampsia in their first pregnancy and 113 normotensive gravid women were studied. All subjects were Japanese women with singleton gestations. Genomic DNA was extracted, and genotypes of angiotensinogen (AGT), methyleneteterahydofolate reductase (MTHFR), factor V Leiden, and prothrombin genes were analyzed.

RESULTS: The frequencies of homozygous AGT gene mutation and homozygous MTHFR gene mutation in preeclampsia were significantly higher than that in control. The calculated risk associated with the presence of both mutations did not exceed the risk with polymorphism of each gene. None of the examined cases showed polymorphism of factor V Leiden and prothrombin G20210A genes.

CONCLUSION: In Japanese patients with preeclampsia, the angiotensinogen gene and particularly MTHFR gene may play a role in the pathogenesis of preeclampsia

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Keywords: Preeclampsia; Polymorphism; Angiotensinogen; Methlenetetrahydrofolate; Factor V; Prothrombin

Introduction

Preeclampsia is a progressive, multisystem disorder unique to pregnant women and is a leading cause of maternal death and contributes significantly to premature deliveries. It is characterized by hypertension and proteinuria, and its incidence is influenced by various factors, such as parity, race, and environmental factors. It is estimated to be about 5~10% in European countries and at 5.8% in first pregnancies and 0.4% in second pregnancies.[1] The etiology of preeclampsia is still unknown, but genetic factors have been implicated since the syndrome shows a familial tendency.[2] Published reports of pedigree analysis suggest that development of preeclampsia may be based on a single recessive gene or dominant gene with incomplete penetrance.[3] However, more recent studies have suggested that the pattern of inheritance is multifactorial and depends on several genetic loci with greater or smaller contributions from environmental factors. In addition, not only maternal gene but also fetal gene may be implicated, and maternal-fetal interaction could not be ignored.

It is unlikely that a particular genotype is involved in the development of preeclampsia. Rather, many loci confer genetic liability that predisposes individuals to the disease. During the last decade, a growing number of genetic variants have been implicated in the development of preeclampsia. To date, reported preeclampsia-related genes are classified in following categolies,

① Renin-Angiotensin system association genes (AGT, Angiotensin II Type 1 Receptor (AGTR1), AGTR1 Agonistic Antibodies, Angiotensin II Type 2 Receptor),

② Endothelial Nitric Oxide Synthase (eNOS),

③ Coagulopathy and Vascular injury genes (MTHFR, Factor V Leiden, Prothrombin),

④ Oxidative Stress Candidate Genes (Lipoprotein Lipase, Apolipoprotein E), and

⑤ Immunoregulatory Candidate Genes (HLA, TNF-α).

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