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Early partial hydatidiform mole: prevalence, histopathology, DNA ploidy, and persistence rate

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Abstract The widespread use of ultrasound in the diagnosis and management of intrauterine fetal death has resulted in moles being evacuated earlier than before. In order to clarify clinicopathologic features of early partial mole (PM), morphology and DNA ploidy of early (≤12 gestational weeks) and late (>12 gestational weeks) partial PM were studied. A total of 80 early and 20 late PMs (37 from 1981–90; 63 from 1991–98) were analyzed. Mean gestational ages were 9.6 weeks for early PMs and 14.8 weeks for late PMs. Early PM was more common in 1991–1998 (57/63, 90%) than in 1981–1990 (23/37, 62%). Pre-evacuation diagnosis of hydatidiform mole was achieved in only 4 early and 1 late PMs. There were no significant differences in histology between early and late PMs, except that villi were smaller in early PMs and there was extensive stromal fibrosis in late PMs. Ploidy was as follows: 70 of 80 early PMs and 19 of 20 late PMs were triploid, 5 early PMs were aneuploid, and 5 early and 1 late PM were diploid. None of 45 patients with early PM and 1 of 11 with late triploid PM developed persistent gestational trophoblastic disease. Early PM is now more prevalent than it was previously. This may be a result of greater awareness of the entity of PM, its increased recognition by pathologists and the widespread use of ultrasound in the diagnosis and management of intrauterine fetal death. The diagnosis of PM should be based on pathological examination, since most PMs still elude clinical detection. DNA ploidy analysis is useful in the evaluation of problem cases. The risk of persistent disease seems to be very low in the case of early PMs.

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Introduction

It is said that the widespread use of ultrasound in the diagnosis and management of molar pregnancies has resulted in moles being evacuated earlier than before. This may be true in cases of complete hydatidiform mole (CM), but it is not clear in cases of partial hydatidiform mole (PM). Clinicopathologic studies of early (gestational age 12 weeks or less) PM have rarely been reported [1, 2, 8, 17]. Here, clinicopathologic features of early PMs are described, and the results of histology, DNA ploidy and persistence rate are reported.

Materials and methods

Cases

One hundred cases of PMs were identified in the surgical pathology files of the Jikei University Hospital and its affiliated hospitals between 1981 and 1998: 37 cases were from between 1981 and 1990 and 63 were from between 1991 and 1998. Material was obtained from spontaneous abortions or from curettages carried out after the detection of intrauterine death or hydatidiform mole by ultrasound examination. Part of this study has already been reported elsewhere [4]. PM at gestational age 12 weeks or less was defined as early PM, and PM at gestational age more than 12 weeks as late PM in this study.

The patients' ages with early PM and late PM ranged from 17 to 43 (mean 29.2) years and from 19 to 40 (mean 28.9) years, respectively. The gestational ages ranged from 7 to 12 weeks (mean 9.6 weeks) for early PM and from 13 to 20 weeks (mean 14.9 weeks) for late PMs.

Histopathologic studies

Routine 4-μm sections of all specimens (one to five blocks from each case), which were stained with hematoxylin-eosin (HE), were reviewed. The diagnosis of molar pregnancy was based on the pathological criteria of Szulman and Surti [20]: the diagnosis of PM was made when there was partial villous involvement (normal

and edematous villi), the presence of an embryo or fetus, mild to moderate focal trophoblastic hyperplasia, and 'trophoblastic inclusion.' Trophoblastic hyperplasia is an essential feature in differentiation of PMs from simple hydropic abortions. The diagnosis of CM was made when there was complete hydatidiform change from edema to central cistern formation, absence of an embryo, and conspicuous trophoblastic hyperplasia. The vesicle size for each case was measured on the histological slides.

DNA analysis

Flow-cytometric DNA analysis was performed on formalin-fixed, paraffin-embedded tissue blocks. The selection criterion for the blocks was the presence of both placental and maternal (decidual) tissue in such amounts that representative DNA histograms could be anticipated. Maternal tissue had to be present as the internal diploid control. A total of 115 blocks (one to three blocks from each placental tissue specimen) was analyzed. The technique of Hedley et al. [10] was used for DNA analysis, with some minor modifications [6].

No karyotypic analysis was performed in diploid or aneuploid PM.

Clinical follow-up

Follow-up after molar evacuation included urine β-human chorionic gonadotropin (hCG) titers measured every week until 12 weeks or serum β-hCG titers measured every week until negative. A diagnosis of persistent trophoblastic disease was determined by inappropriate falling of urine β-hCG, or rising serum β-hCG, or a plateau of previously falling β-hCG based on three consecutive titers during the follow-up after molar evacuation.

Results

Histopathological studies

Table 1 summarizes histological features of early and late PMs. PMs showed the following features: villous vesicular edema often associated with attenuated trophoblastic layers (Fig. 1), villous scalloping (Figs. 1, 2) and focal mild to moderate syncytiotrophoblastic hyperplasia (Figs. 3, 4). These were observed in all cases. Additional features of the villi were cistern formation (Figs. 1, 2) in 99 cases (99%), presence of trophoblastic inclusions (Fig. 2) in 99, presence of fetal blood cells in 86, nucleated red blood cells (Fig. 4) in 72 and fetal parts in 18. Wandering trophoblasts in the villous stroma were seen in 41 and extensive stromal fibrosis was observed in 11. Size of villi in early PMs ranged from 1.2 to 6.2 mm (mean, 3.0 mm), while the villi in late PMs ranged from 1.5 to 6.5 (mean 3.4 mm) in size. There were no significant differences in histology except the smaller villi in early PMs (P=0.046) and the presence of extensive stromal fibrosis in late PMs (P=0.003; Fig. 5). There was also no significant difference in histology among triploid, diploid and aneuploid (nontriploid/tetraploid) PMs.

Clinical data

Pre-evacuation diagnosis of mole was achieved in 4 of the 80 patients with early PM and in 1 of the 20 with late PM. Follow-up information was available in 45 patients with early PM and 11 with late PM. One patient with late PM (gestational age of 17 weeks) developed persistent gestational trophoblastic disease, in which residual molar material in the uterus was histologically confirmed, and received chemotherapy. No sequelae were encountered following the patients with early PM.

DNA analysis

The mean coefficient of variation of the G0/G1 peak for all cases examined ranged from 2.1% to 7.93% (mean 4.63%). The DNA indexes of the triploid peak were between 1.38 and 1.60. Most (79 of 80 early PMs and 19 of 20 late PMs) of the PMs were DNA triploid; 5 early PMs were aneuploid, while 5 early and 1 late PM were diploid.

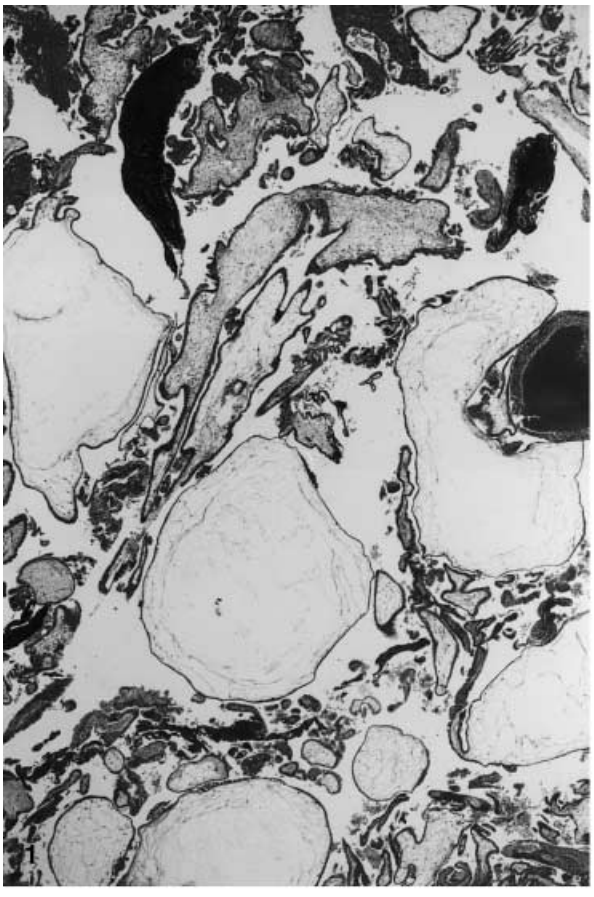
Discussion

This study indicated that early PM is now more prevalent than it was previously. This does not mean an increase in its incidence. First, it is probably a result of greater awareness of the entity of PM and its increased recognition by pathologists. Secondly, it may also be due to the widespread use of ultrasound in the diagnosis and management of intrauterine fetal deaths, in some cases of which histological study discloses PM. In general, pa-

Table 1 Histology of early and late partial moles

	Early partial mole n=80 (%)	Late partial mole n=20 (%)
Villous edema	80 (100)	20 (100)
Cistern formation	79 (99)	20 (100)
Focal syncytiotrophoblastic hyperplasia	80 (100)	20 (100)
Villous scalloping	80 (100)	20 (100)
Trophoblastic inclusion	79 (99)	20 (100)
Nucleated red blood cells	57 (71)	15 (75)
Fetal parts	15 (19)	3 (15)
Fetal blood vessels	67 (84)	19 (95)
Extensive stromal fibrosis	2 (3)§	9 (45)§
Wandering trophoblast	32 (40)	9 (45)
Maximal size of villi (mm)[a]	1.2–6.2	1.5–6.5
Mean size of villi (mm)[a]	3.0 § §	3.4 § §

§ P=0.003; § § P=0.046 (statistically significant differences)
[a]Measured on histological slides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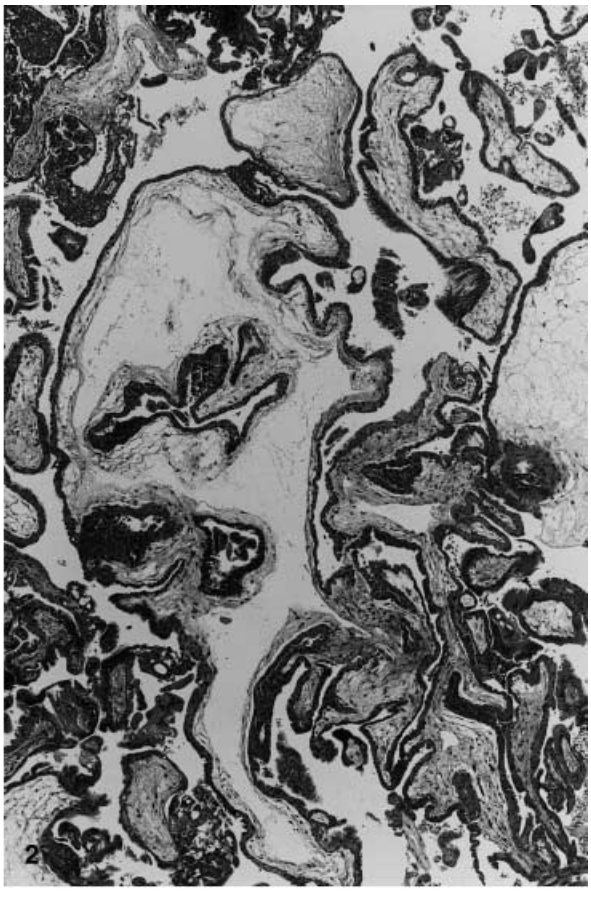
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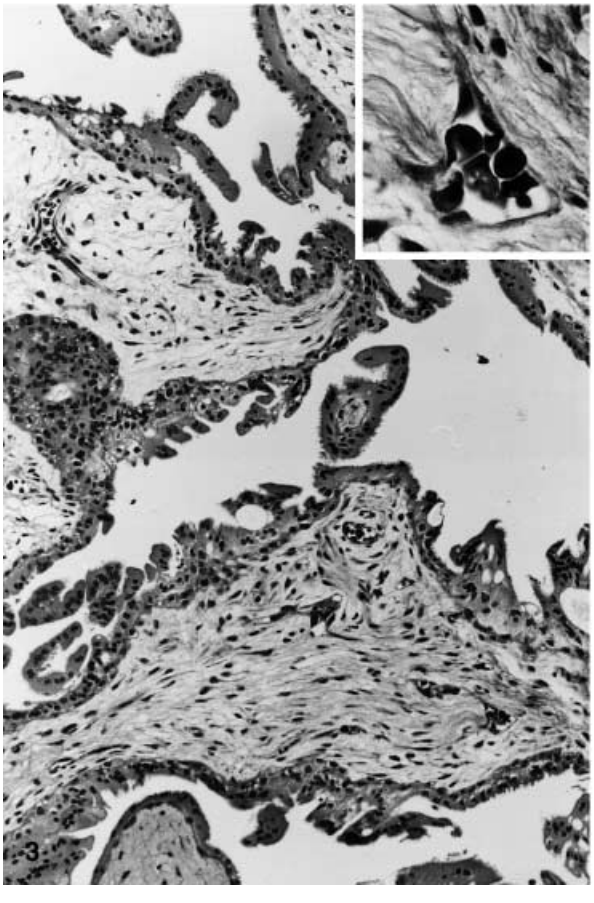
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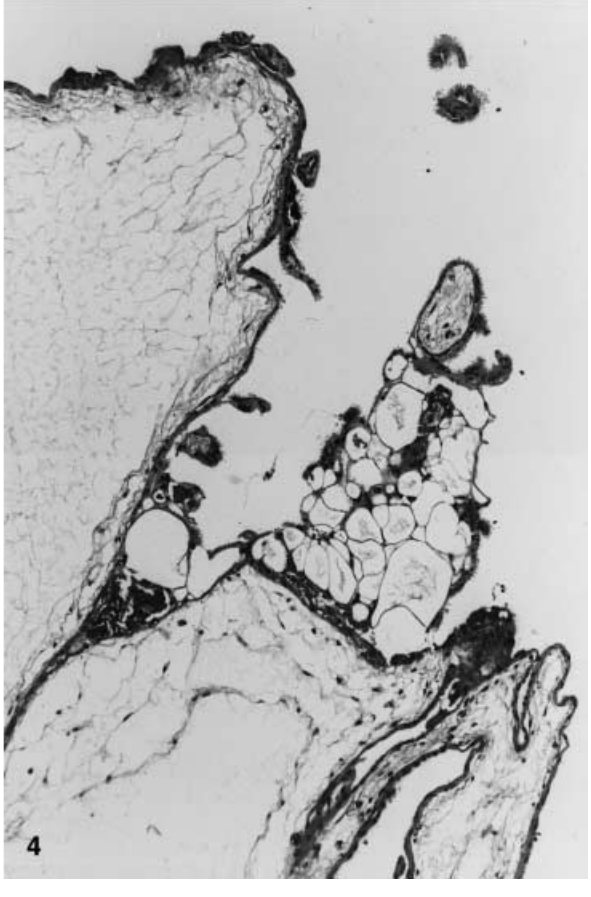
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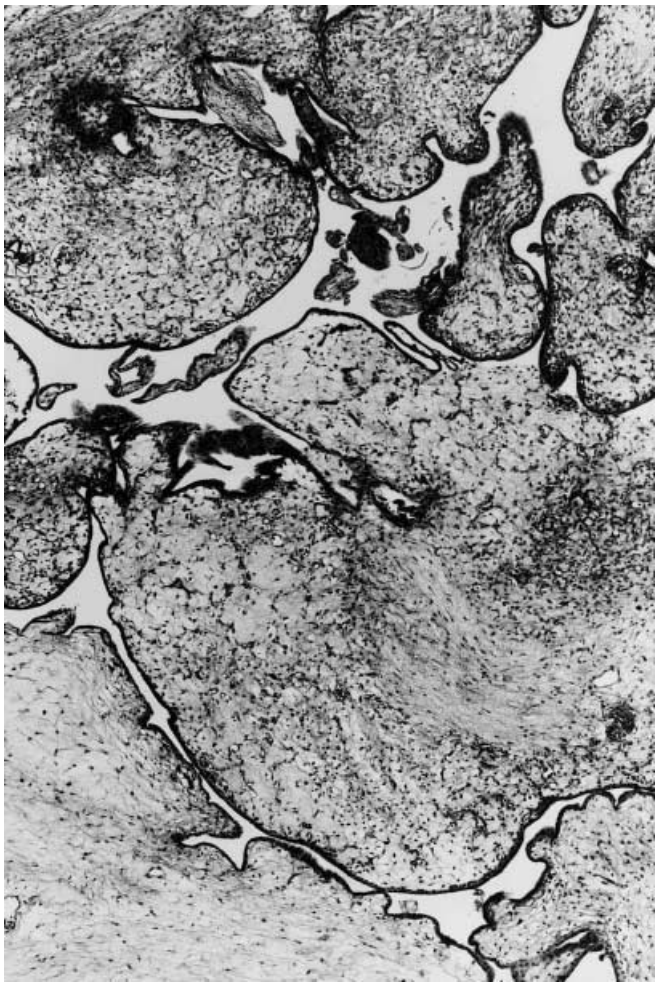

Fig. 5 Triploid late partial mole at 17th gestational week showing enlarged villi with extensive stromal fibrosis. HE, ×40

tients with PM present with the signs and symptoms of incomplete or missed abortion. Since pre-evacuation diagnosis of hydatidiform mole was achieved in only 4 of the 80 patients with early PM and only 1 of the 20 with late PM in this study, the diagnosis of PM is usually made after a histological review of curettage specimens. Ultrasound examination may not be sensitive enough to detect early PMs that have not fully evolved. The diagnosis of PM by ultrasound is less accurate than is the case with CMs [2, 3].

There were no significant differences between early and late PMs in histology except the smaller villi in early PMs and the extensive stromal fibrosis in late PMs. PM is an underdiagnosed condition because histopathological evaluation of the degree of trophoblastic hyperplasia and of villous hydropic swelling is subjective [7, 11]. First, early PMs must be histologically distinguished from hydropic abortions. The most frequent clinical diagnosis in both hydropic abortion and PM is that of spontaneous abortion [4]. Hydropic abortions are usually evacuated earlier than PMs and CMs [17]. PMs are characterized by the dual villous populations consisting of normal-sized villi and irregular, enlarged villi. The presence of focal syncytiotrophoblastic hyperplasia with vacuolization and scalloping also helps to discriminate early PM from hydropic abortion [7, 8]. In hydropic abortions, villous edema is mild to moderate and it is generally focal and occasionally diffuse with ballooning outlines. The covering trophoblast layers are markedly attenuated without trophoblastic hyperplasia. Redline et al. [18] recently reported that trophoblastic hyperplasia, equivalent to that seen with typical proliferative partial and complete moles, was frequently observed in spontaneous abortions with trisomy 7, 15, 21, or 22, and that these spontaneous abortions lacked uniformly hydropic villi and fetal tissue. However, our previous study [5] indicated that no trophoblastic hyperplasia was observed in any case with trisomy. It also indicated that first trimester placental tissues with abnormal karyotypes often showed villous hydropic changes. Mild to moderate villous edema, hypo- or avascular stroma and cistern formation, which are often observed in both hydropic abortions and PMs, may be regressing changes. PM should not be diagnosed solely on the basis of villous size. Stromal fibrosis is always observed in placental tissues from second trimester abortuses, and sometimes in early spontaneous abortions.

Secondly, early PMs should be distinguished from early CMs, which involve a higher risk of persistent disease. Sheikh and Lage [19] mentioned that only a minority of early CMs had gross vesicles. According to the study by Keep et al. [12], histological diagnostic features of early CMs are redundant bulbous terminal villi, hypercellular villous stroma, a labyrinthine network of villous stromal canaliculi, focal cytotrophoblast and syncytiotrophoblast hyperplasia on both villi and the undersurface of the chorionic plate and enlarged hyperchromatic implantation site trophoblast. Interestingly, Sheikh and Lage [19] observed persisting vessels with nucleated red blood cells in some early CMs, but no fetal parts were present. However, I have never encountered any CM with nucleated red blood cells except in a twin gestation. PMs are histologically different from early CMs in the absence of redundant bulbous terminal villi with hypercellular villous stroma. Trophoblastic hyperplasia in early CMs is usually more prominent than that in PMs. Most CMs are diploid or tetraploid [2, 15].

◀ **Fig. 1** Triploid early partial mole at the 12th gestational week, showing focal vesicular edema of the villi with attenuated trophoblastic layers, villous scalloping, and cistern formation. Focal trophoblastic hyperplasia was observed in other fields. HE, ×20

Fig. 2 Triploid early partial mole at the 12th gestational week, showing villous scalloping, cistern formation, focal mild to moderate trophoblastic hyperplasia, and trophoblastic inclusions. HE, ×40

Fig. 3 Triploid early partial mole at the 11th gestational week, showing villous scalloping, a trophoblastic inclusion, and fetal blood vessels. HE, ×200 *Inset*: Nucleated red blood cells are observed in fetal blood vessels. HE, ×400

Fig. 4 Triploid early partial mole at the 9th gestational week, showing focal syncytiotrophoblastic hyperplasia with vacuolation, attenuated trophoblastic layers and cistern formation. HE, ×200

DNA flow-cytometric analysis is helpful in differential diagnosis of PMs [4, 7, 8, 15]. Most hydropic abortions are diploid [8]. Although most of the late PMs and many of the early PMs were triploid, some early PMs were diploid or aneuploid. No significant histological differences were seen between the triploid and nontriploid PMs in this study. Lage et al. [13, 15] reported PMs with diploid, haploid, aneuploid and tetraploid DNA content. Therefore, ploidy or genetic heterogeneity among PMs is suggested, and cytogenetic analysis is essential as well as careful histological examination for the diagnosis of nontriploid PM. Practically, histological differentiation between PM and hydropic abortion is extremely difficult in some placental tissues, and follow-up with measurement of serum or urine hCG titers is required in these cases. It is clear that morphological criteria as currently defined are an unreliable basis for a firm diagnosis of PM, especially in less obvious cases. There is an urgent need to establish stricter, quantitative, criteria for the evaluation of trophoblastic hyperplasia, such as the number of cell layers, whether focal or circumferential hyperplasia is present, and the minimal number of villi involved.

In the current study, although the number of cases was small, all patients with early PMs whose follow-up data were available had spontaneous resolution. The risk of persistent disease seems to be very low in early PMs. There was no correlation between DNA ploidy status and clinical outcome of patients with PMs in the present study. It is assumed that PM is not a neoplasm but a kind of abortion modified by degeneration. Ohama et al. [16] suggest that a PM with aneuploid karyotype has little tendency to invade and metastasize and usually requires no therapy other than evacuation. In contrast, a case of choriocarcinoma following a triploid PM has been reported [9], and Lage et al. [14] have reported triploid PMs with persistent trophoblastic disease. Since the true biological potential of triploid PM is still unclear, follow-up with measurement of hCG titers is required for patients with triploid PM. Flow-cytometric analysis, cytogenetic investigation, and analyses of restriction fragment length polymorphisms will surely contribute to the confirmation of a pathological diagnosis, yielding information on characteristics related to the persistent disease, which cannot always be obtained by macroscopic or microscopic inspection.

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References

1. Chew SH, Ronnett B, Williams R, Kurman RJ, Periman EJ (1998) Morphology and DNA content in the evaluation of firsts trimester placentas for partial hydatidiform mole (PHM) (abstract). Mod Pathol 11:102A
2. Conran RM, Hitchcock CL, Popek EJ, Norris HJ, Griffin JL, Geissel A McCarthy WF (1993) Diagnostic considerations in molar gestations. Hum Pathol 24:41–48
3. Fox H (1997) Differential diagnosis of hydatidiform moles. Gen Diagn Pathol 143:117–125
4. Fukunaga M (1994) Histopathologic study of partial hydatidiform moles and DNA triploid placentas. Pathol Int 44: 528–534
5. Fukunaga M, Onda T, Endo Y, Ushigome S (1995) Is there a correlation between histology and karyotype in early spontaneous abortion? Int J Surg Pathol l2:295–300
6. Fukunaga M, Silverberg SG (1990) Kaposi's sarcoma in patients with acquired immune deficiency syndrome: a flow cytometric DNA analysis of 26 lesions in 21 patients. Cancer 66:758–764
7. Fukunaga M, Ushigome S, Endo Y (1995) Incidence of hydatidiform mole in a Tokyo hospital: a 5-year (1989 to 1993) prospective, morphological and flow cytometric study. Hum Pathol 26:758–764
8. Fukunaga M, Ushigome S, Fukunaga M, Sugishita M (1993) Application of flow cytometry in diagnosis of hydatidiform moles. Mod Pathol 6:353–359
9. Gardner HAR, Lage JM (1992) Choriocarcinoma following a partial hydatidiform mole: a case report. Hum Pathol 23: 468–471
10. Hedley DW, Friedlander M, Taylor IW, Rugg CA, Musgrove EA (1983) Method for analysis of cellular DNA content of paraffin-embedded pathological material using flow cytometry. J Histochem Cytochem 31:1333–1335
11. Jeffers MD, O'Dwyer P, Leader BCM, Gillan JE (1993) Partial hydatidiform mole: a common but underdiagnosed condition. A 3-year retrospective clinicopathological and DNA flow cytometric analysis. Int J Gynecol Pathol 12:315–331
12. Keep D, Zaragoza MV, Hassold T, Redline WR (1996) Very early complete hydatidiform mole. Hum Pathol 27:708–713
13. Lage JM, Weinberg DS, Yavner DL, Bieber FR (1989) The biology of tetraploid hydatidiform moles. Histopathology, cytogenetics, and flow cytometry. Hum Pathol 20:419–425
14. Lage JM, Berkowitz RS, Rice LW, Goldstein DP, Bernstein MR, Winberg DS (1991) Flow cytometic analysis of DNA content in partial hydatidiform moles with persistent gestational trophoblastic tumor. Obstet Gynecol 77:111–115
15. Lage JM, Mark SD, Roberts DJ, Goldstein DP, Bernstein MR, Berkowitz RS (1992) A flow cytometric study of 137 fresh hydropic placentas; correlation between types of hydatidiform moles and nuclear DNA ploidy. Obstet Gynecol 79:403–410
16. Ohama K, Ueda K, Okamoto E, Takenaka M, Fujiwara A (1986) Cytogenetic and clinicopathologic studies of partial moles. Obstet Gynecol 68:259–262
17. Paradinas JF, Browne P, Fisher RA, Foskett M, Bagshawe KD, Newlands E (1996) A clinical, histopathological and flow cytometric study of 149 complete moles, 146 partial moles and 107 non-molar hydropic abortions. Histopathology 28: 101–109
18. Redline RW, Hassold T, Zaragoza M (1998) Determinants of villous trophoblastic hyperplasia in spontaneous abortions. Mod Pathol 11:762–768
19. Sheikh SS, Lage JM (1998) Diagnosis of early complete hydatidiform mole (ECM): a study of 35 cases. Mod Pathol 11:114A (abstract)
20. Szulman AE, Surti U (1978) The syndromes of hydatidiform mole. II. Morphologic evolution of the complete and partial mole. Am J Obstet Gynecol 132:20–27