

# Comparative Cytogenetic and Clinicopathologic Studies on Gestational Trophoblastic Neoplasia, especially Hydatidiform Mole

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*Hydatidiform mole has been known for its potential for malignant transformation and for its various chromosomal karyotypes. However, the relationship between histologic grading of hydatidiform mole and its future malignant transformation is still controversial. This study was undertaken to determine the cytogenetic aspects of gestational trophoblastic neoplasia, especially of hydatidiform mole with respect to its malignant transformation. Cytogenetic studies were performed in 34 cases of hydatidiform mole, 2 cases of invasive mole, and 2 cases of choriocarcinoma. The results were analyzed comparatively using clinical, histopathological and endocrinological (human chorionic gonadotropin titer) data. Among the 34 cases of hydatidiform mole studied, 26 cases were complete moles and the remaining 8 were partial moles with karyotypes being diploid (46,XX,24,46,XY,2), and triploid (69,XXY) respectively. Two cases of XX mole among 26 complete hydatidiform moles developed distant metastasis during the follow-ups, suggesting transformation into choriocarcinoma; both cases showed 46,XX in karyotype and Grade III in histologic grading. Not one case of triploid partial hydatidiform mole transformed into malignancy. The karyotypes of the two cases each of invasive mole and choriocarcinoma were from neardiploid to hypotetraploid, and aneuploid cells were predominant in choriocarcinoma.*

**Key Words:** Complete hydatidiform mole, Partial hydatidiform mole, Beta Subunit-Human chorionic gonadotropin (B-H.C.G.), Karyotype.

With the recent advent of modern research techniques in cytogenetics, the chromosomes of tumor cells can now be accurately karyotyped, and the comparison of chromosomes between benign and malignant cells has become possible.

To explain malignant transformation, human chorionic lesions, namely hydatidiform mole, invasive mole, and choriocarcinoma, have been the subject of intense scrutiny.

Hydatidiform mole exhibits several chromosomal karyotypes and exhibits a potential for malignant transformation.

Previous chromosome analysis of hydatidiform moles has shown mostly 46,XX, diploidy (Sasaki *et al.* 1962; Makino *et al.* 1963, 1965), and rarely triploidy

(Atkin and Klinger 1962; Makino *et al.* 1964).

In 1964 Makino *et al.*, and subsequently Carr in 1969, suggested an association between hydatidiform mole and triploidy, and a certain correlation between hydatidiform degeneration and hydatidiform moles.

Vassilakos and Kajii (1976) reclassified molar pregnancy into two entities; complete hydatidiform mole and partial hydatidiform mole.

Since then, partial hydatidiform mole has been regarded as a distinct entity. Unfortunately however, not much information has been published about its clinical and cytogenetic features.

Triploid molar abortion can be a favorable sign (Levy *et al.* 1972; Poland and Baillie 1978), while aneuploid hydatidiform mole as reported may give a grave prognosis. The karyotype can give us a guiding basis for the treatment of hydatidiform mole (Husslein 1967). There is considerable difference of opinion regarding the relationship between the histologic grading of the trophoblast and subsequent malignant transformation. Some investigators have found a good correlation between increased hyperplasia and malignant transformation (Hertig and Scheldon 1947; Her-

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tig and Mansell 1956; Schiffer *et al.* 1960), while others reported no such relationship (Hunt *et al.* 1953; Elston and Bagshawe 1972).

Serial human chorionic gonadotropin (HCG) titrations is a method used to screen patients for detection of malignant transformation in hydatidiform moles (Goldstein and Kosasa 1976; Schlaerth *et al.* 1981; Smith *et al.* 1984).

In hydatidiform degeneration of the placenta exhibiting a triploid chromosome constitution, human chorionic gonadotropin levels are frequently elevated to values between detected in normal placentas and in hydatidiform moles (Paterson *et al.* 1971; Wertelecki *et al.* 1976).

This study was undertaken to determine the cytogenetic aspects of gestational trophoblastic neoplasia, particularly of hydatidiform mole in view of malignant transformation by comparative analysis of their clinical, histopathological and endocrinological data.

## MATERIALS AND METHODS

Of 14,849 deliveries, 275 cases diagnosed as gestational trophoblastic neoplasia were evaluated during the period from January, 1, 1979 to December, 31, 1985 at the department of Obstetrics and Gynecology, Yonsei University Medical Center.

Satisfactory karyotyping and clinical follow-ups were possible in 26 cases of complete hydatidiform mole, 8 cases of partial hydatidiform mole, 2 cases of invasive mole, and 2 cases of choriocarcinoma.

Cytogenetic studies were done by tissue culture and/or direct preparation method. The specimens were under sterile conditions by curettage or hysterectomy and were promptly sent to the cytogenetic laboratory. The molar tissue was separated from surrounding placental tissues under a dissecting microscope.

To prepare the tissue culture, the isolated specimen was washed two to three times with Hanks' balanced salt solution in a sterile petri-dish, then minced with scissors. The tissue was then evenly divided among several 50ml TC flasks to which were added Eagles minimum essential medium (MEM, GIBCO) plus 20% fetal calf serum and antibiotics. The cultures were then placed in a CO<sub>2</sub> incubator at 37°C. The cultures were monitored under an inverted microscope until the mitotic rate was sufficiently high enough to warrant harvest. The average culture time was about four weeks. Harvesting and metaphase preparation were done according to routine techniques.

For direct harvest, the fresh specimen was washed in Hank's balanced salt solution, minced with scissors and placed in 100mm petri-dish containing 10ml of MEM culture medium added with 0.05μg per milliliter colcemid. Following a one hour incubation under CO<sub>2</sub> at 37°C, the culture was treated with 2ml of a 0.075M potassium chloride hypotonic solution for 20 minutes at 37°C. The cells then were fixed with 3:1 mixture of methanol and acetic acid and the cell suspension was dropped on clean slides and air-dried.

The slides were stained with Giemsa solution, examined for chromosomes in metaphase which were photographed and karyotyped.

In conjunction with the cytogenetic study, some portions of the specimens were fixed with formalin for histologic diagnosis and grading. Hematoxylin and Eosin stain was used to classify the cells into grade I, II, and III according to the degrees of trophoblastic hyperplasia (Hertig and Mansell 1956).

HCG levels were determined prior to treatment and during follow-up by the following methods: B-H.C.G. (Serono H.C.G. radioimmunoassay kit, sensitivity less than 4 mIU/ml), (LH radioimmunoassay kit, sensitivity less than 25 mIU/ml), 24 hour urine collection for H.C.G. titer (international unit/L), and Gravindex (Pregnancy test, sensitivity above 500 mIU/L).

## RESULTS

### A. Clinical data

**Incidence:** The incidence of gestational trophoblastic neoplasia was 1 in 54 deliveries. Among the gestational trophoblastic neoplasia studied, the incidence of hydatidiform mole was 1 in 93 deliveries (Table 1).

**Maternal data:** In terms of maternal age and parity, no significant difference was noted between com-

**Table 1. Incidence of gestational trophoblastic neoplasia in Yonsei University Medical Center (1979-1985)**

|                       | No. of cases | Cases/deliveries |
|-----------------------|--------------|------------------|
| Total delivery        | 14,849       |                  |
| Trophoblastic disease | 275          | 1 / 54           |
| Hydatidiform mole     | 159          | 1 / 93           |
| Invasive mole         | 17           | 1 / 873          |
| Choriocarcinoma       | 99           | 1 / 150          |

Table 2. Clinical data, cytogenetic &amp; histoenocrinologic studies on complete hydatidiform mole

| Case No. | Maternal age (yr) | Obstetric history | Gestation weeks | Mode of evacuation | Trophoblastic histologic grading | Cytogenetic analysis  | HCG levels              |                            | HCG normal weeks after evacuation | Chemotherapy      | Reason for treatment   |
|----------|-------------------|-------------------|-----------------|--------------------|----------------------------------|-----------------------|-------------------------|----------------------------|-----------------------------------|-------------------|--|
|          |                   |                   |                 |                    |                                  |                       | Before evacuation       | 2-6 weeks after evacuation |                                   |                   |  |
| 1        | 29                | G1P0A0            | 25              | D & C              | I                                | 46,XX                 | 88,000 IU               | Gravindex(-)               | 18                                | Act D, MTX        | Prophylactic   |
| 2        | 28                | G3P1A0            | 13              | D & C              | III                              | 46,XX                 | 13,500 IU               | Gravindex(-)               | 25                                | Act D, MAC        | Rebound of HCG, delayed decrease of HCG, lung metastasis                     |
| 3        | 32                | G2P1A0            | uncertain       | D & C              | I                                | 46,XX                 | 11,850 IU               | 5m IU                      | 8                                 | —                 | —  |
| 4        | 28                | G2P1A0            | 18              | D & C              | I                                | 46,XX                 | 14,834 mIU              | 2,984m IU                  | 21                                | Act D             | Delayed decrease of HCG  |
| 5        | 50                | G6P3A3            | uncertain       | TAH                | I                                | 46,XX                 | 12,800 IU<br>93,625m IU | 2,386m IU                  | no follow up                      | —                 | —  |
| 6        | 30                | G2P1A0            | 13              | D & C              | I                                | 46,XX                 | 64,000 IU<br>18,103m IU | 102m IU                    | 20                                | MTX<br>CF         | Delayed decrease of HCG  |
| 7        | 49                | G8P6A2            | 12              | D & C<br>TAH       | III                              | 46,XX with aneuploidy | 1,248,000 IU            | 24m IU                     | 16                                | Act D             | Prophylactic   |
| 8        | 25                | G2P1A0            | 14              | D & C              | II                               | 46,XX                 | 112,000 IU              | 75m IU                     | no follow up                      | Act D             | Prophylactic   |
| 9        | 24                | G1P0A0            | 16              | D & C              | II                               | 46,XY                 | 94,400 IU               | > 200m IU                  | 19                                | MTX, CF           | Delayed decrease of HCG  |
| 10       | 33                | G3P1A1            | 12              | D & C              | II                               | 46,XX                 | 176,000 IU              | 124m IU                    | 15                                | Act D             | Prophylactic   |
| 11       | 26                | G1P0A0            | 12              | D & C              | II                               | 46,XX                 | 1,515,520 IU            | 116m IU                    | 16                                | Act D             | Prophylactic   |
| 12       | 37                | G6P1A4            | 9               | D & C              | II                               | 46,XX with aneuploidy | 45,470 IU               | 1,746 m IU                 | 30                                | Act D<br>MTX      | Prophylactic, delayed decrease of HCG  |
| 13       | 33                | G2P0A1            | 13              | D & C              | II                               | 46,XX                 | 5,925 IU                | 70m IU                     | 20                                | Act D             | Prophylactic   |
| 14       | 21                | G1P0A0            | 11              | D & C              | II                               | 46,XX                 | 20,500 IU               | 100m IU                    | 4                                 | —                 | —  |
| 15       | 24                | G2P0A1            | 18              | D & C              | I                                | 46,XX                 | 308,000 IU              | 24 hour urine(-)           | 3                                 | Act D             | Prophylactic   |
| 16       | 46                | G9P7A1            | 8               | TAH                | I                                | 46,XX                 | 102,400 IU              | 24 hour urine(-)           | 3                                 | Act D             | Prophylactic   |
| 17       | 49                | G7P5A1            | uncertain       | TAH                | II                               | 46,XX                 | 7,500 IU                | 196m IU                    | 13                                | —                 | —  |
| 18       | 28                | G1P0A0            | 11              | D & C              | III                              | 46,XX                 | 256,000 IU              | 6,950 IU                   | —                                 | MTX, Act D<br>MAC | Rebound of HCG, delayed decrease of HCG, lung and liver metastasis (expired) |
| 19       | 22                | G2P0A1            | 12              | D & C              | III                              | 46,XX                 | 81,920 IU<br>40,000m IU | 160m IU                    | 17                                | Act D             | Prophylactic   |
| 20       | 22                | G1P0A0            | 11              | D & C              | I                                | 46,XX                 | Gravindex(+)            | 45m IU                     | no follow up                      | Act D             | Prophylactic   |
| 21       | 27                | G2P0A1            | 27              | D & C              | I                                | 46,XX                 | Gravindex(+)            | Gravindex(-)               | 22                                | —                 | —  |
| 22       | 27                | G2P1A0            | 23              | D & C              | III                              | 46,XX                 | 84,000 IU               | 64 m IU (LH)               | 11                                | —                 | —  |
| 23       | 27                | G4P1A2            | 16              | D & C              | II                               | 46,XX                 | 108,640 IU              | 82m IU                     | 13                                | —                 | —  |
| 24       | 29                | G2P1A0            | 16              | D & C              | I                                | 46,XY                 | 243,200 IU              | 15m IU                     | 11                                | Act D             | Prophylactic   |
| 25       | 29                | G2P1A0            | 28              | D & C              | I                                | 46,XX                 | > 200m IU               | Gravindex(-)               | 13                                | Act D             | Prophylactic   |
| 26       | 23                | G1P0A0            | 15              | D & C              | II                               | 46,XX                 | 214,040 IU<br>88,960 IU | 29m IU                     | 9                                 | Act D             | Prophylactic   |

G, gravida; P, para; A, previous abortion; D & C, Dilatation and curettage; TAH, Hysterectomy; Serum levels in milli-international units per milliliter; Urine levels in international units per liter; Gravindex, pregnancy test; Act D, Actinomycin D; MTX, Methotrexate; CF, Citrovorum factor; MAC, Methotrexate Actinomycin D and Cytosine.

**Table 3. Clinical data, cytogenetic & histoendocrinologic studies on partial hydatidiform mole**

| Case No. | Maternal age (yr) | Obstetric history | Gestation weeks | Mode of evacuation | Trophoblastic histologic grading | Cytogenetic analysis | HCG levels        |                            | HCG normal weeks after evacuation | Chemo-therapy | Reason for treatment |
|----------|-------------------|-------------------|-----------------|--------------------|----------------------------------|----------------------|-------------------|----------------------------|-----------------------------------|---------------|----------------------|
|          |                   |                   |                 |                    |                                  |                      | Before evacuation | 2-6 weeks after evacuation |                                   |               |                      |
| 1        | 28                | G1P0A0            | 23              | D & C              | II                               | 69,XXY               | 16,000 IU         | 90m IU (LH)                | no follow up                      | —             | —                    |
| 2        | 29                | G2P1A0            | 20              | D & C              | I                                | 69,XXY               | Gravindex(+)      | Gravindex(-)               | 23                                | —             | —                    |
| 3        | 26                | G11P1A9           | 28              | D & C              | I                                | 69,XXY               | > 200m IU         | 3m IU                      | 3                                 | —             | —                    |
| 4        | 27                | G3P1A1            | 26              | D & C              | I                                | 69,XXY               | Gravindex(+)      | 19m IU(LH)                 | 4                                 | —             | —                    |
| 5        | 20                | G1P0A0            | 6               | D & C              | I                                | 69,XXY               | Gravindex(+)      | 4550 IU                    | no follow up                      | Act D         | prophylactic         |
| 6        | 44                | G12P8A3           | 21              | D & C              | I                                | 69,XXY               | 24 hour urine(-)  | 70m IU(LH)                 | 5                                 | —             | —                    |
| 7        | 23                | G1P0A0            | 21              | D & C              | I                                | 69,XXY               | 24 hour urine(-)  | Gravindex(-)               | 6                                 | Act D         | Prophylactic         |
| 8        | 31                | G3P2A0            | 25              | D & C              | I                                | 69,XXY               | Gravindex(-)      | —                          | no follow up                      | —             | —                    |

**Table 4. Clinical data, cytogenetic & histologic studies on chorioadenoma destruens and choriocarcinoma**

| Case No. | Maternal age (yr) | Obstetric history | Histologic evidence of specimen | Cytogenetic analysis       | Trophoblastic histologic grading | Metastasis   | Treatment and follow up  |
|----------|-------------------|-------------------|---------------------------------|----------------------------|----------------------------------|--|--|
| 1        | 43                | G10P6A3           | Chorioadenoma destruens         | neardiploid-hypotetraploid | Apparently Malignant (III)       | Rt. Parametrium<br>Rt. Infundibulo-pelvic ligament | T.A.H. with B.S.O  |
| 2        | 44                | G5P2A3            | Chorioadenoma destruens         | neardiploid-hypotetraploid | Apparently malignant (III)       | Rt. Parametrium                                    | T.A.H. with B.S.O.   |
| 3        | 25                | G3P1A1            | Choriocarcinoma                 | neardiploid-hypotetraploid | Apparently Malignant (III)       | Lung, Brain, liver, terminal ileum                 | Segmental resection of ileum.<br>radiation (brain)<br>chemotherapy |
| 4        | 47                | G5P4A1            | Choriocarcinoma                 | neardiploid-hypotetraploid | Apparently malignant (III)       | Vagina   | Chemotherapy   |

T.A.H with B.S.O., Total abdominal hysterectomy with Bilateral salpingoophorectomy

plete hydatidiform mole and partial hydatidiform mole.

Partial hydatidiform mole had a longer gestational period with a mean of 21.3 weeks, than the complete hydatidiform mole which had a mean of 15.3 weeks (Tables 2, 3).

### B. Cytogenetic and histo-endocrinologic studies

All 26 cases of complete hydatidiform mole were diploid in karyotype; 24 cases (92.3%) were 46,XX including 2 cases of 46,XX with aneuploid (neardiploid) and 2 other cases (7.7%) were 46, XY (Table 2). All 8 cases of partial hydatidiform mole were triploid (69, XXY) in karyotype (Table 3). Two cases each of invasive mole and choriocarcinoma were from neardiploid to hypotetraploid in karyotype and aneuploid cells were

predominant in choriocarcinoma (Table 4 and Fig. 1).

The levels of preevacuation B-HCG were higher in diploid complete hydatidiform mole than in triploid partial hydatidiform mole. The mean regression time of postevacuation H.C.G. level was 14.4 weeks and 8.2 weeks for complete and partial hydatidiform moles respectively (Figs. 2 and 3, Tables 2 and 3).

Of the complete hydatidiform mole group, 2 cases of 46,XX with aneuploidy (neardiploid) mole (cases 7 and 12), serum B-HCG showed the longest mean regression time to normal by 23.0 weeks (Figs. 4 and 5) implying higher potential for malignant transformation.

The mean regression time of XY mole was longer with 15 weeks than in XX mole with 14.3 weeks but the difference was not statistically significant (P<.05)

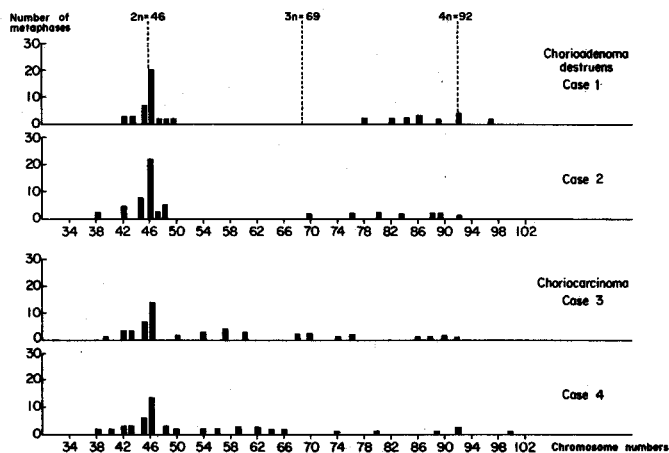


Fig. 1. Distributions of chromosome-numbers in chorioadenoma destruens and choriocarcinoma.

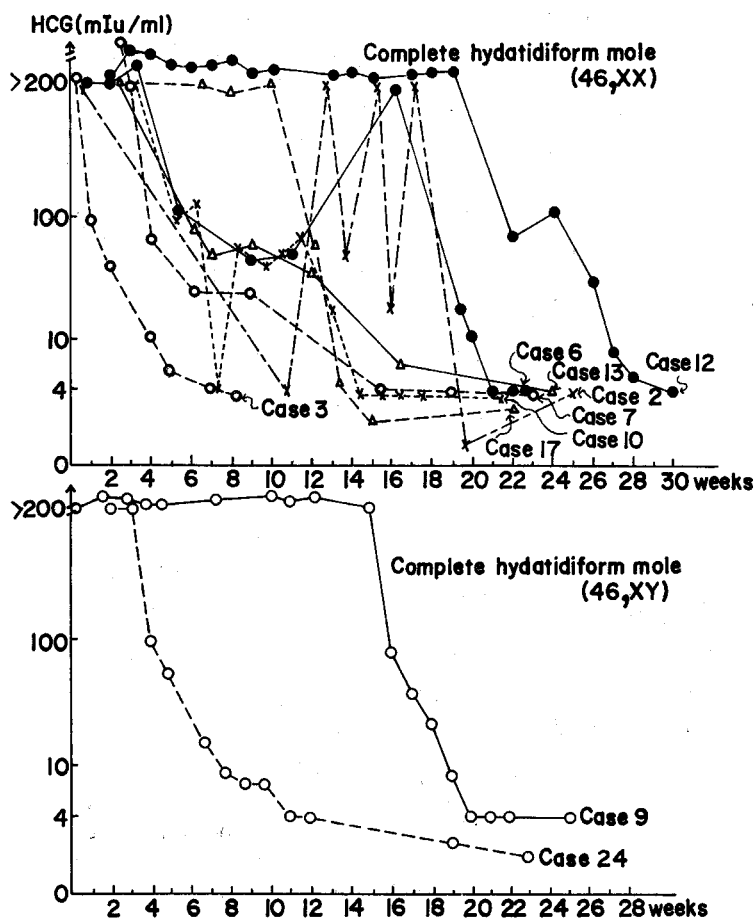


Fig. 2. Graph summarized HCG regression curve in 10 complete hydatidiform mole (8 cases of 46,XX, 2 cases of 46,XY) patients by HCG beta-subunit radioimmunoassay.

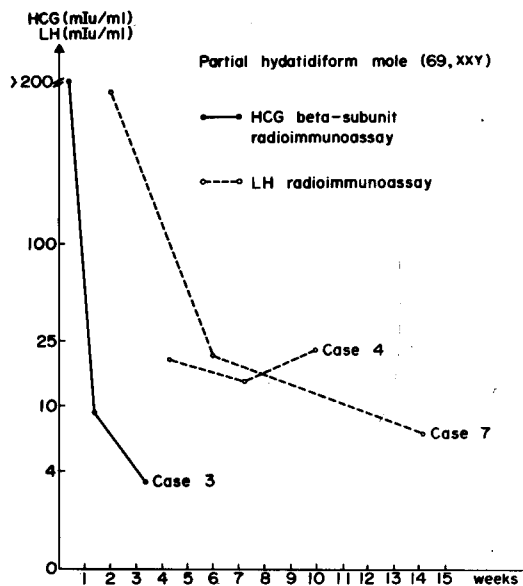


Fig. 3. Graph summarized regression curve in 3 partial hydatidiform mole (69,XXY) patients.

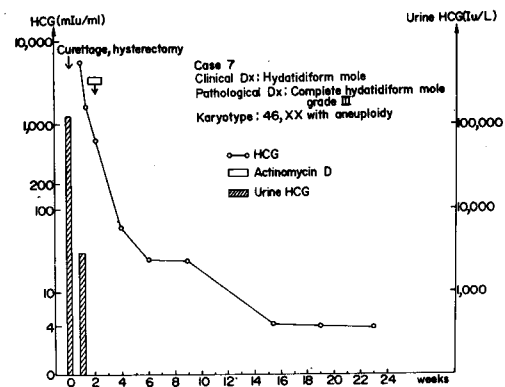


Fig. 4. Case 7. HCG regression curve in 49 year old patient with complete hydatidiform mole showing 46,XX with aneuploidy in karyotype.

(Table 2 and Fig. 2). The histological grading of 26 cases of complete hydatidiform mole classified 11 cases (42.3%) as Grade I, 10 cases (38.5%) as Grade II, and 5 cases (19.2%) as Grade III (Figs. A,B,C). Two of these cases were 46,XX with aneuploidy (near diploid); one was case 7 with Grade III and the other was case 12 with Grade II.

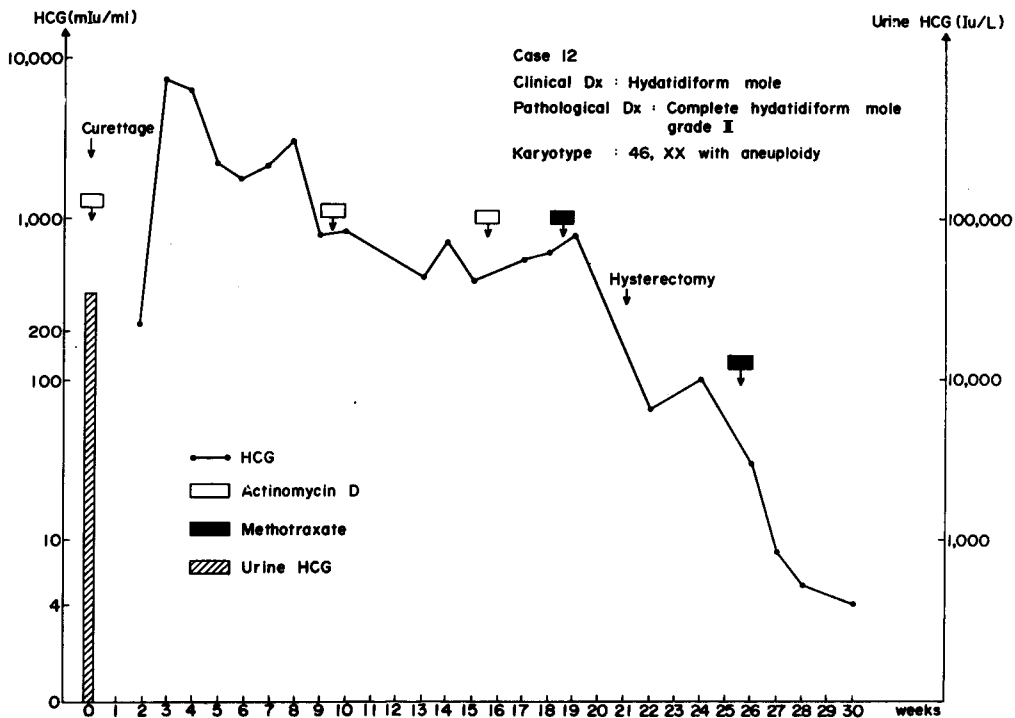


Fig. 5. Case 12. HCG regression curve in 37 year old patient with complete hydatidiform mole who showed 46, XX with aneuploidy in karyotype.

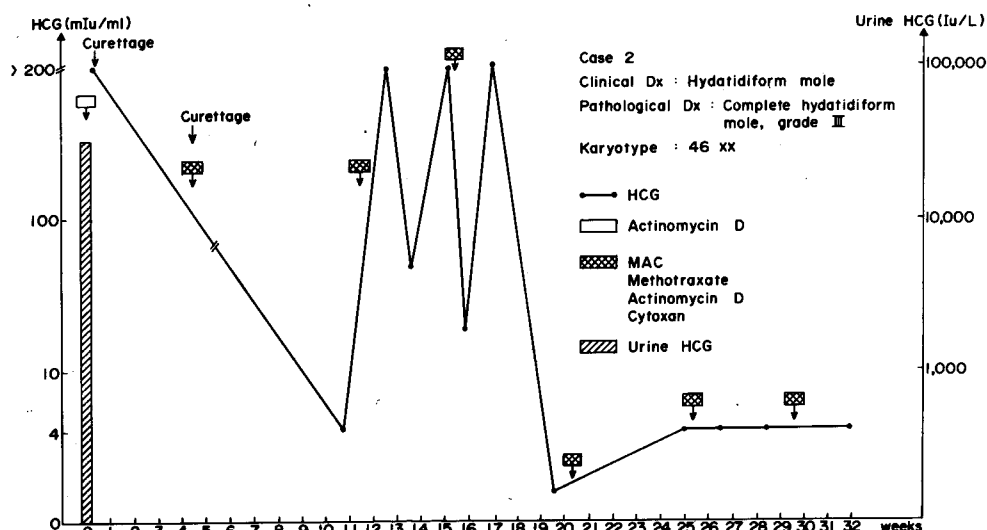


Fig. 6. Case 2. HCG regression curve in 28 year old patient with complete hydatidiform mole who developed lung metastasis.

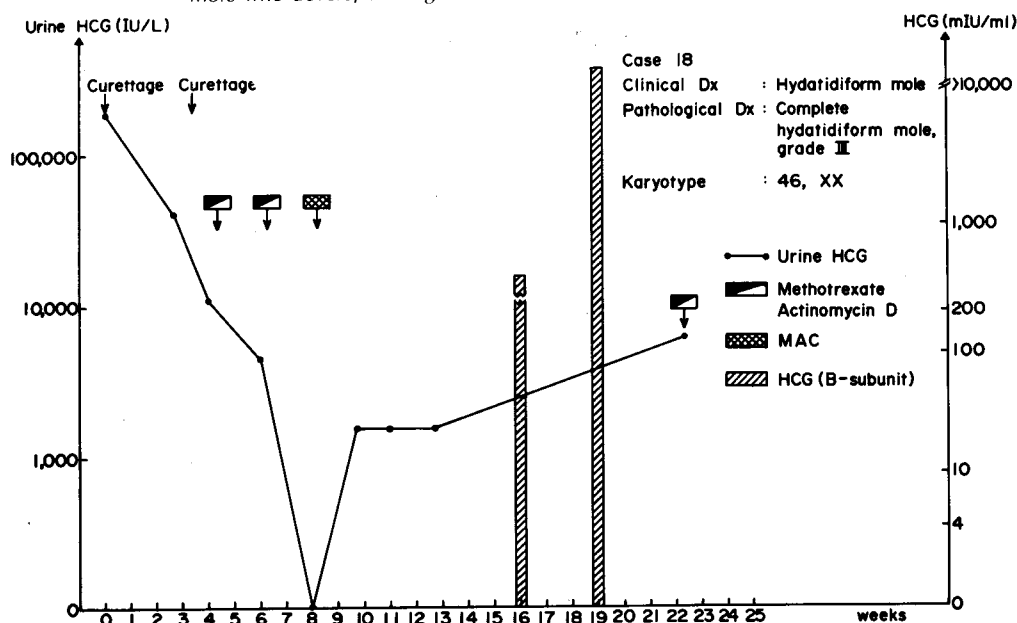


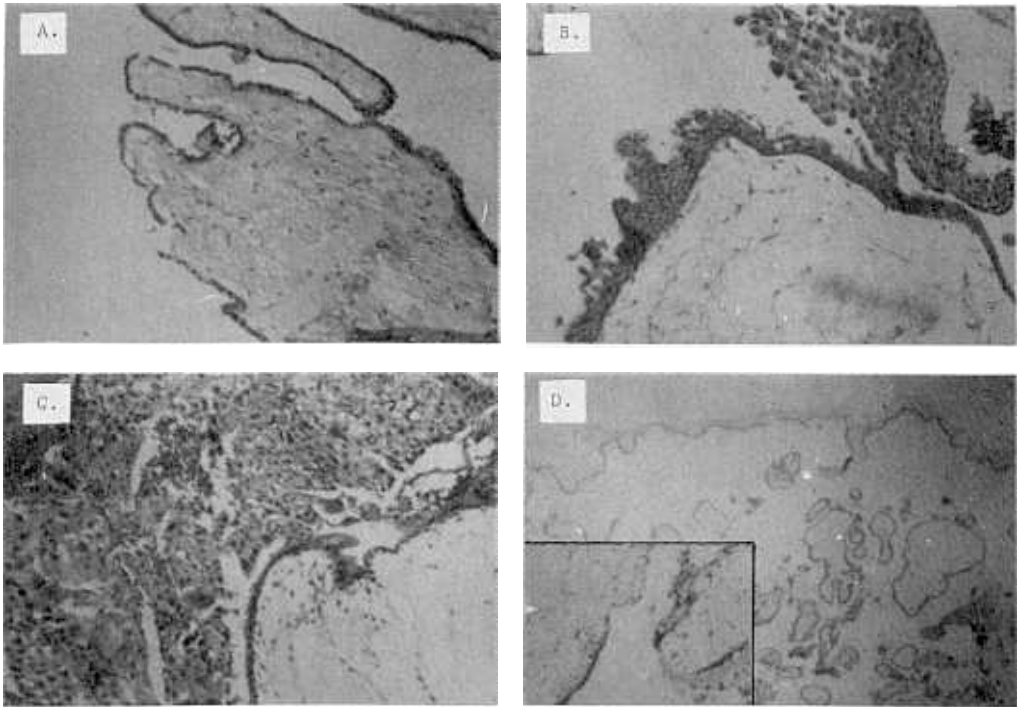
Fig. 7. Case 18. HCG regression curve in 28 year old patient, with complete hydatidiform mole who developed lung and liver metastasis and died.

Two cases of 46,XY mole present (case 9 and case 24) were graded as II and I respectively.

Of eight partial moles of triploid (69, XXY) karyotype, seven were Grade I (Fig. D) and one was Grade II.

The mean regression time was prolonged in those cases exhibiting a higher histological grading. In Grade

I, II and III of the complete hydatidiform mole group the mean regression time was 12.1 weeks, 15.4 weeks, and 17.3 weeks respectively. However, no statistically significant difference was present among them. Two cases of 26 complete hydatidiform moles developed distant metastasis during the follow-up, suggesting transformation into choriocarcinoma: both



- Fig. A.** Complete hydatidiform mole, 25 weeks menstrual age; 46 XX, Case 1, Grade I. Photomicrograph showing enlarged cystic villi lined by trophoblasts with mild proliferation. (H & E,  $\times 100$ )
- Fig. B.** Complete hydatidiform mole, 13 weeks menstrual age; 46 XX, Case 13, Grade II. Photomicrograph showing moderate trophoblastic hyperplasia with relatively nuclear uniformity. (H & E,  $\times 100$ )
- Fig. C.** Complete hydatidiform mole, 13 weeks menstrual age; 46 XX with aneuploidy, Case 7, Grade III. Photomicrograph showing marked trophoblastic hyperplasia with nuclear variability. (H & E,  $\times 100$ )
- Fig. D.** Partial hydatidiform mole, 6 weeks menstrual age; 69 XXY, Case 5, Grade I. Photomicrograph showing numerous relatively small villi with early hydatidiform change and somewhat vascularized stroma (H & E,  $\times 25$ ) Inset: A fragment of chorionic plate at the top. (H & E,  $\times 100$ )

cases (cases 2 and 18; Figs. 6 and 7) were 46,XX and Grade III. However, no malignant transformation was noted in any of the triploid partial hydatidiform moles.

## DISCUSSION

The possibility of a relationship between chromosome change and malignant transformation was first hypothesized by Boveri. This view was later supported by other researchers (Richart and Ludwig 1969; Miles 1975).

In order to understand malignant transformation of benign tumors, researchers have often focused on human chorionic villi with emphasis on the pathogenesis of hydatidiform mole, invasive mole, and choriocarcinoma.

Makino *et al.* (1965) in their study on chromosome

change and malignant transformation of hydatidiform mole proposed that normal villi progressively change into hydatidiform mole, chorioepithelioma, and choriocarcinoma.

Moles had historically been described as classic (true) hydatidiform moles, transitional moles, incomplete moles, and occasional moles. Following the developed of sophisticated chromosome studies, accompanied by the advanced in the histological study of chorionic tissue, hydatidiform mole has been reclassified into two distinct groups: complete hydatidiform mole and partial hydatidiform mole (Vassilakos and Kajii 1976; Vassilakos *et al.* 1977).

Complete hydatidiform moles have no identifiable fetal or embryonic tissues. The chorionic villi have generalized hydatidiform swelling and are diffusely enveloped by hyperplastic and atypical trophoblasts.

In contrast, partial hydatidiform moles are

characterized by identifiable embryonic or fetal tissues, variably sized chorionic villi with focal hydatidiform swelling and cavitation, focal trophoblastic hyperplasia, marked scalloping of chorionic villi and prominent trophoblastic inclusions in the stroma of chorionic villi (Szulma and Surti 1978; Czer-nobilsky 1982; Berkowitz *et al.* 1986).

In our study of complete hydatidiform moles hyperplasia of trophoblasts was also observed in both layers of cytotrophoblasts and syncytiotrophoblasts, but neither fetal red blood cells nor amniotic membrane were identified. In partial hydatidiform mole, the hydropic change was limited to some portions of the villi, and the hyperplasia of the trophoblast was confined to syncytiotrophoblasts. Fetal red cells, amniotic membrane and chorionic plate were observed.

The incidence of gestational trophoblastic neoplasia shows racial and regional variance; it is much higher in the Far eastern countries than in the Western countries (Bagshawe 1969; Novak *et al.* 1975). The incidence of complete hydatidiform mole has been reported as 1 in 2,500 deliveries (Novak *et al.* 1975), and 1 in 1,699 deliveries (Brewer *et al.* 1971), whereas in partial hydatidiform mole, it has been reported as 1 in 22,000 deliveries, 1 in 2,875 abortions and 1 in 20 hydatidiform moles (Jones and Lauersen 1975).

Our study showed 1 hydatidiform mole in 93 deliveries. This high incidence was probably due to the fact that we are a referral hospital.

Controversy still exists concerning the relationship between trophoblastic grading and subsequent malignant change. Studies by (Hertig and Sheldon 1947; Hertig and Mansell 1956; Schiffer *et al.* 1960) support a good relationship between them, while others regarded histological grading as of doubtful value or showing no such relationship (Hunt *et al.* 1953; Elston and Bagshaw 1972; Bagshawe 1976).

In this study the two cases (cases 2 and 18) of complete hydatidiform mole which transformed into choriocarcinoma were Grade III. The mean regression time of post-evacuation HCG titer in complete hydatidiform mole showed a progressively delaying pattern of 12.1, 15.4 and 17.3 weeks for Grade I, II and III respectively, although this pattern was not statistically significant ( $p < .05$ ), it does indicate a trend deserving further research. Two cases each of invasive mole and choriocarcinoma were also Grade III.

Chromosome analysis of the classic hydatidiform moles revealed exclusively female karyotype, 46,XX, (Sasaki *et al.* 1962; Makino *et al.* 1965), whereas transitional mole or hydatidiform degeneration showed a preponderance of polypoidy, especially of triploidy

(Makino *et al.* 1964; Carr 1969).

Following the classification of hydatidiform mole into complete mole and partial mole, various studies on the karyotypes of hydatidiform moles were conducted and the results showed that complete hydatidiform moles were mostly diploid (Vassilakos and Kajii 1976; Vassilakos *et al.* 1977; Surti *et al.* 1979; Davis *et al.* 1984; Kajii *et al.* 1984).

In partial hydatidiform mole, the triploid karyotype predominated (Vassilakos *et al.* 1977) with the most common type being 69, XXY, the next being 69, XXX, and then 69, XYY.

Occasionally diploid karyotypes (Teng and Ballon 1984) or even tetraploids (Surti *et al.* 1986), and trisomy (Vasilakos *et al.* 1977) were also reported.

Karyotyping in this study showed that all 26 cases of complete hydatidiform mole were diploid; 24 XX moles including 2 cases of 46,XX with aneuploid (near-diploid), and 2 XY moles (7.7%). The 8 cases of partial hydatidiform mole were all triploid (69, XXY).

Tsuji *et al.* (1981) reported that in 2 cases of invasive mole and 1 case of choriocarcinoma, the distribution of chromosome number was diploidy (2n), 30%; aneuploidy of 2n to 4n, 58%; tetraploidy (4n), 3%; and aneuploidy of over 4n, 9%. Aneuploid cells were predominant in these cases.

In our study 2 cases each of invasive mole and choriocarcinoma showed from neardiploid to hypo-tetraploid in karyotype, and aneuploid cells appeared to be more predominant in choriocarcinoma than in invasive mole.

In general the prognosis of hydatidiform mole depends on many factors; among them are the histopathology, the levels of H.C.G., and the presence or absence of metastasis to other organs (Bagshawe 1976; Kohorn 1982; Surwit *et al.* 1984). In hydatidiform mole, H.C.G. levels have been widely employed in determining therapeutic effects and prognosis (Goldstein and Kosasa 1976; Morrow *et al.* 1977; Schlaerth *et al.* 1981; Goldstein and Berkowitz 1982; Smith *et al.* 1984).

With clinicopathological study alone, Czernobilsky *et al.* (1982) found transition rates of 4.2% to invasive mole and 2.1% to choriocarcinoma from complete hydatidiform mole, but no malignant change from partial hydatidiform mole. Szulman and Surti (1982) reported one malignant transformation from 13 partial hydatidiform moles. Berkowitz *et al.* (1979) also reported one (3%) patient with a partial mole developing persistent gestational trophoblastic tumor with local uterine invasion which required chemotherapy for remission.

Interestingly, Teng and Ballon (1984) reported 3

cases of partial hydatidiform mole with diploid karyotype which was not in line with the general view that partial hydatidiform mole was triploid. They contended that the partial mole with normal diploid karyotype should be considered a distinct clinical entity with the potential for malignant sequelae.

Surti *et al.* (1979) and Davis *et al.* (1984) reported the incidence of XY mole to be 1 to 3% and 8.1% respectively.

Surti *et al.* (1982) and Wake *et al.* (1984) each claimed that diploid complete hydatidiform moles with XY karyotype carried higher a incidence of malignant transformation than those with XX karyotype.

In our study no malignant transformation of XY complete hydatidiform moles (case 9, Grade II, case 24, Grade I) was noted. The mean regression time of HCG was longer than XX mole which however showed no statistical significance ( $P < .05$ ).

Two cases of 26 complete hydatidiform moles developed distant metastasis during the follow-ups suggesting transformation into choriocarcinoma: One case (case 2, 46,XX, Grade III) showed a rebound, a delayed decrease of HCG, and then a lung metastasis despite chemotherapy. The other one (case 18, 46,XX, Grade III) also showed a rebound, a delayed decrease of HCG, but then developed lung and liver metastases and in spite of vigorous chemotherapy, died. In this study, not a single case of triploid partial hydatidiform mole transformed into malignancy.

It has been noted that the higher the levels of preevacuation H.C.G. in hydatidiform mole, the longer it takes for the HCG level to regress to normal (Smith *et al.* 1984).

Our study revealed the mean serum B-H.C.G. level to be higher in complete hydatidiform mole than in partial hydatidiform mole. The longest period of regression was 23.0 weeks by two 46,XX with aneuploid (neartriploid) complete hydatidiform moles (cases 7 and 12), while the shortest regression period achieved by a triploid partial hydatidiform mole was 8.2 weeks.

Of the 2 cases of 46,XX with aneuploid mole, cases 7 and 12 exhibited a delayed decrease of HCG. Case 7 was that of a 49 year old woman with a Grade III 46,XX aneuploid mole who had been treated as follows: curettage, hysterectomy, and chemotherapy with actinomycin D. This was given due to the woman's age and her high initial titer of HCG. Case 12, a 37 year old with a Grade II condition, was treated with curettage and four courses of chemotherapy. The latter necessitated a subsequent hysterectomy followed by an additional course of chemotherapy in order to normalize the levels of HCG.

Tsuji *et al.* (1981) reported that hydatidiform mole in older women were frequently aneuploid, which they believed were related to the increased potential for local invasion and metastasis. However, there was one case in the younger age group in which in tissue with aneuploid cells apparently persisted and later developed into choriocarcinoma.

Our results seem to suggest that aneuploid hydatidiform moles have a higher potential for malignant transformation. It is therefore advisable to manage aneuploid hydatidiform mole with active treatment and careful clinical follow-up.

These results suggest that the potential for malignant transformation of hydatidiform mole may be present in diploid and/or diploid with aneuploid karyotypes, but not in the triploid karyotypes. It is therefore important in the former group to provide close follow-up and appropriate therapy after evacuation of hydatidiform mole.

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