BULLETIN OF TAIPEI MEDICAL COLLEGE, VOL. 15, MAY 1986
P. 127-135

Follow-up Study on Destructive Mole and Choriocarcinoma During the Past Thirty Years (1947-1976) in Taiwan

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ABSTRACT

Gestational trophoblastic disease was not a rare disease in Taiwan. Choriocarcinoma was usually fatal in the pre-chemotherapeutic era, and it was very similar to destructive mole in clinical and pathological fields, but the prognosis after hysterectomy was quite different. This difference attracted the author to study on this topic about 30 years ago.

Each histopathological diagnosis of gestational trophoblastic disease from surgical specimens was very difficult even for experienced pathologists without adequate specimens and clinical information. The more accurate diagnosis of gestational trophoblastic disease from surgical specimens needed the intimate cooperation between clinicians and pathologists.

The purposes of this study were to obtain the results of follow-up in cases of destructive mole and choriocarcinoma during the past thirty years in Taiwan.

Key words: Gestational trophoblastic disease, Hydatidiform mole, Destructive mole (Invasive mole), Choriocarcinoma, Methotrexate (MTX)

MATERIAL AND METHOD

The material used in this study consists of surgical specimens and autopsy materials of trophoblastic disease collected at Departments of Pathology of National Taiwan University Hospital (1947-1966) and Taipei Medical College (1967-1976) during the past 30 years (1947-1976).

The trophoblastic disease was diagnosed based on morphology and classified into hydatidiform mole, destructive mole and choriocarcinoma. The diagnostic criteria are discribed as follows:

1. **Hydatidiform mole (non-invasive mole):**

Specimen: Usually, it can be diagnosed by uterine curettage.

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Received for Publication: January 23, 1986.

Gross examination: Numerous noticeable molar vesicles in the specimen submitted.

Clinic: There should be no vaginal or lung metastasis at the time of the first curetting. The case of simultaneous metastasis or so-called "benign metastasizing mole" is included in the invasive mole.

Microscopic examination: Numerous large hydropic villi, avascularity or scantiness of blood vessels in the villous stroma, proliferation of trophoblasts can be seen.

2. **Destructive mole (invasive mole):**

Specimen: As a general rule, the diagnosis should be made by whole hysterectomized uterus or excised vaginal or other metastatic lesions. Diagnosis only by curettage is almost impossible unless it contains pieces of myometrial tissue with evidence of myometrial or vascular invasion.

t **Gross examination:** Invasive mole in the myometrium which usually is seen as a withish spongy nodule with or without hemorrhage. (Empty uterus with extra-uterine metastasis should keep in mind.)

Microscopic examination: Deep invasion of myometrium or blood vessels with presence of villi embedded in the sheet of proliferating trophoblastic cells are seen. The same picture can be seen as in the excised metastatic lesion elsewhere.

3. **Choriocarcinoma:**

Specimen: As a general rule, it can be diagnosed only by whole hysterectomized uterus (with some exceptional cases, such as empty uterus with extra-uterine metastatic choriocarcinoma). The diagnosis made by excised metastatic lesion or uterine curetting is uncertain.

Gross examination: Hemorrhagic bulky tumor mass in the uterine cavity (rarely empty uterus with extra-uterine metastastic choriocarcinoma is present as mentioned above).

Microscopic examination: Diffuse sheets of trophoblastic cells with extensive hemorrhagic necrosis and no villi present.

Those cases which lacked adequate slides and specimens or clinical data were excluded during the period between 1947-1966. But, the incomplete biopsy specimens were adopted as uncertain cases during the period between 1967-1976.

After re-evaluation of the microscopic slides, gross specimens and clinical data according to our diagnostic criteria, 809 cases of trophoblastic disease including 518 cases of hydatidiform mole, 126 cases of destructive mole, 142 cases of choriocarcinoma and 23 uncertain cases were selected.

The follow-up study consists of 3 series with variable follow periods from 6 months to more than 5 years. The result of the 1st series (the period during 1947-1956) was reported on Reports, Institute of Pathology of National Taiwan University[1] in 1957. The result of the 2nd series (1957-1966) was reported on Acta Pathologica Japonica[2] in 1967. The result of the 3rd series (1967-1976) was made a special speech at the 70th Annal Meeting of the Formosan Medical Association on Nov. 11, 1977, without publication in any journal. The present report was

collected the results of these 3 series and 91 cases of destructive mole and 94 cases of choriocarcinoma were available for follow-up study.

Types of antecedent pregnancy of 95 cases of choriocarcinoma and 100 cases of destructive mole were also collected for the present report.

RESULTS AND DISCUSSION

1. Cases

809 cases of gestastional trophoblastic disease including 518 cases of hydatidiform mole, 126 cases of destructive mole, 142 cases of choriocarcinoma and 23 uncertain cases were collected during the past 30 years between 1947-1976, based on morphologic diagnoses (Table 1). The uncertain cases were adopted during the period between 1967-1976, due to those incomplete specimens being submitted. The excised lesions showed only a few trophoblastic cells without villi, so they were uncertain to be diagnosed as destructive mole or choriocarcinoma.

2. Age Distribution

The age distribution of patient in destructive mole was from 18 to 55 years old and in choriocarcinoma from 18 to 61 years old (Table 2). Most of cases were within age group between 20 and 50 years, rarely under age of 20 years and over age of 50 years. Highest peak is between 20 to 30 years both in Destructive mole and choriocarcinoma. According to Novak and Seah's[3] series, Highest peak of choriocarcinoma is in the same age group of between 20 to 30 years. But, in their series, most of choriocarcinoma were the age group of under the 30 years, 66% (49 cases/74 cases), and over 30 years were 34% (25 cases/74 cases), while in our series, 62% (88 cases/142 cases) of choriocarcinoma were in the age group of over 30 years and 36% (51 cases/142 cases) were the age group of under 30 years. In Taiwan, choriocarcinoma seems to be more often seen in the older age group of over 30 years. It is quite different from Novak and Seah's[3] series.

Table 1. 809 Cases of Gestational Trophoblastic Desease Collected During the Past Thirty Years (1947-1976)

Year	GTD uncertain	HM	DM	CC	total
1947-1956 NTUH			22	35	57
1957-1966		228	70	57	355
1967-1976 TMPC	23	290	34	50	397
Total	23	518	126	142	809

GTD : gestational trophoblastic disease
DM : destructive mole
NTUH: National Taiwan University Hospital
HM : hydatidiform mole
CC : choriocarcinoma
TPMC: Taipei Medical College

Table 2. Age Distribution of Destructive Mole and Choriocarcinoma During Past Thirty Years (1947-1976)

Years	below 20	20-30	31-40	41-50	51-60	over 60	unknown	Total
DM	2	55	33	33	3	1		126
CC	4	47	43	37	7	1	3	142
Total	6	102	76	70	10	1	3	268

DM: Destructive mole
CC : Choriocarcinoma

Table 3. Type of Antecedent Pregnancy in Choriocarcinoma and Destructive Mole (1947-1976)

Antecedent pregnancy	Choriocarcinoma No. of cases (%)	Destructive Mole No. of cases (%)	Total (%)
Hydatidiform mole	52 (54.7)	93 (93)	145 (74.4)
Abortion	21 (22.1)	7 (7)	28 (14.4)
Normal pregnancy	18 (19)		18 (9.2)
Tubal pregnancy	4 (4.2)		4 (2.0)
Total	95	100	195

3. Antecedent Pregnancy

95 cases of choriocarcinoma and 100 cases of destructive mole were available for this study. Of 95 cases of choriocarcinoma, 52 cases (54.7%) followed hydatidiform mole, 21 cases (22.1%) followed abortion, 18 cases (19%) followed normal pregnancy, and 4 cases (4.2%) followed tubal pregnancy. 93 cases of hydatidiform mole (93%) and 7 cases of abortion (7%) preceded in 100 cases of destructive mole (Table 3). 37 to 78%[3,4,5,6] of choriocarcinoma cases and 98[7] to 100%[4] of destructive mole cases being preceded by hydatidiform mole were reported in the literature. The 7% of abortion preceding destructive mole in our series may be due to inaccurate statement by the patients themselves.

4. Follow-up Study

It was difficult to follow the cases of gestational trophoblastic disease in Taiwan in the past years, especially those cases collected at Department of Pathology, Taipei Medical College, to where most of specimens were submitted by daily busy practitioners in this island. Therefore, 91 cases of destructive mole and 94 cases of choriocarcinoma were available for follow-up study.

(1) Results of 91 cases of destructive mole

The mortality rate in the 1st series (1947-1956) was 6.3% (1 case/16 cases); the 2nd series, 9.7% (6 cases /62 cases); the 3rd series (1967-1976), 15.4% (2 cases/ 13 cases), respectively. The overall mortality rate was 9.9% (9 cases/91 cases) for destructive mole (Table 4). As compared with

those series reported in the literature, the mortality rate ranged from 3.6 to 14.3%[7,8,9] for cases of destructive mole treated by surgery without methotrexate.

No mortality rate in case of Destructive mole treated by Methotrexate is reported in the literature[16].

But, in our series, one case of Destructive mole died during post-operative chemotherapy by Methotrexate in the 3rd series during 1967-1976.

The mortality rate was increased in the 3rd series of this report, it may be due to a small series as compared with those the other two series.

The causes of death in our 9 cases of destructive mole were recurrence, massive hemorrhage, pulmonary metastases, brain metastases, generalized metastases and pulmonary T.B., according to the clinical data. Only one case of destructive mole in our series, having developed generalized metastases 9 months after total hysterectomy and adnexectomy, was proved to be a case of destructive mole progressing to choriocarcinoma by autopsy.

Besides, complications in form of uterine perforation were not rare. 4 cases developing uterine perforation were also noted in our series.

(2) Results of 94 cases of choriocarcinoma

The mortality rates were 88.8% (22 cases/25 cases) in the 1st series (1947-1956), 55.6% (25 cases/45 cases) in the 2nd series (1957-1966), and 50% (12 cases/24 cases) in the 3rd series (1967-1976), respectively. The overall mortality rate was 62.8% (59 cases/94 cases) (Table 5).

Methods of treatment, metastases and metastatic sites were important factors in determining prognosis of choriocarcinoma. The mortality rates for choriocarcinoma diagnosed by morphology, ranged from 40.3 to 75.8%[3,4,10,11,14] been reported in the literature. The mortality rates for choriocarcinoma treated by sur-

Table 4. Follow-up Study on Destructive Mole (1947-1976)

Years	Alive	Dead	Lost	Total	Mortality rate	Treatment
1947-1956 NTUH	15	1	6	22	6.3%;1/16	Surgery alone
1957-1966 NTUH	56 (6)	6	8	70	9.7%;6/62	Surgery with or without Methotrexate
1967-1976 TPMC	11 (3)	2 (1)	21	34	15.4%;2/13	Surgery with or without Methotrexate
Total	82 (9)	9 (1)	35	126	9.9%;9/91	

( ): cases treated with Methotrexate

$X^2 = 0.681$ D.F. = 2 $P > 0.05$

gery alone ranged from 60.7[11] to 74.2%[10], and the mortality rate in those cases with metastases ranged from 76.9 to 89.1%. In cases of choriocarcinoma treated with methotrecate alone, or with surgery and methotrexate, ranged from 29.6 to 40.8%[10,12] been recorded in the literature. The follow-up periods were varied in the literature, and more reasonable mortality rates would be obtained if the cases could have been followed for longer periods.

(3) Effectiveness of Methotrexate (MTX)

MTX was used for treatment of gestational trophoblastic disease since 1956 in the world[14], and the drug was introduced into Taiwan since 1962[15]. 25 cases of choriocarcinoma were treated with MTX and surgery in our series during 1962-1976, and 7 cases of them were dead. The mortality rate for choriocarcinoma treated with MTX and surgery was 28% (7 cases/25 cases). There were 69 cases of choriocarcinoma treated by only surgery without MTX during 1947-1976, and 52 cases of them were dead, and the mortality rate was 75.4% (Table 6). No significant difference was noted between cases of destructive mole with and without MTX treatment (Table 4). Chemotherapy for

Table 5. Follow-up Study on Choriocarcinoma (1947-1976)

Years	Alive	Dead	Lost	Total	Mortality rate	Treatment
1947-1956 NTUH	3	22	10	35	88.8%;22/25	Surgery alone
1957-1966 NTUH	20 (11)	25 (4)	12	57	55.6%;25/45	Surgery with or without Methotrexate
1967-1976 TPMC	12 (7)	12 (3)	26	50	50% ;12/24	Surgery with or without Methotrexate
Total	35 (18)	59 (7)	48	142	62.8%;59/94	

( ): Cases treated with Methotrexate
$X^2 = 9.486$ D.F. = 2 $P < 0.05$

Table 6. Comparison between Cases of Choriocarcinoma Treated with MTX and without MTX (1947-1976)

	Alive	Dead	Total	Mortality rate
with MTX	18	7	25	28% ; 7/25
without MTX	17	52	69	75.4%;52/69
Total	35	59	94	62.8%;59/94

$X^2 = 17.614$ D.F. = 1 $P < 0.05$

gestational trophoblastic desease was well-developed in recent years[16,17]. No mortality in cases of destructive mole and 81% of remission rate for choriocarcinoma were obtained according to the literature[16].

SUMMARY

809 cases of gestational trophoblastic disease were collected during the past 30 years (1947-1976) at Departments of Pathology, National Taiwan University Hospital (1947-1966) and Taipei Medical College (1967-1976). They included 518 cases of hydatidiform mole, 126 cases of distructive mole, 142 cases of choriocarcinoma and 23 uncertain cases based on morpologic diagnoses. Follow-up study was divided into 3 separated series during this 30 years with variable periods from 6 months to more than 5 years, and data of 91 cases of destructive mole and 94 cases of choriocarcinoma were available. The mortality rates in the 1st series (1947-1956), the 2nd series (1957-1966) and the 3rd series (1967-1976) were 6.3% (1/16), 9.7% (6/62) and 15.4% (2/13) for destructive mole, and 88.8% (22/25), 55.6% (25/45) and 50% (12/24) for choriocarcinoma, respectively. The overall mortality rates were 9.9% (9/91) for destructive mole and 62.8% (59/94) for choriocarcinoma, respectively. The mortality rate for choriocarcinoma was decrease significantly from the period of pure surgical treatment to that of combined surgical and chemotherapeutic treatments, especially treated with Methotrexate, which was introdued into Taiwan since 1962. The mortality rate for destructive mole was slightly increased in the 3rd series, it may be due to a small series as compared with those of the other two series.

There is one case of Destructive mole died during post-operative chemotherapy by Methotrexate in the 3rd series during 1967-1976.

The age distribution of patients in destructive mole varied from age of 18 to 55 years, and in choriocarcinoma from age of 18 to 61 years. Of 142 cases of choriocarcinoma, 88(62%) were in the age group over 30 years, 51(36%) were under age group of 30 years. In Taiwan, choriocarcinoma seems to be more often seen in older age group of over 30 years. This age distribution is quite different from the Novak and Seah's series[3].

Of 95 cases of choriocarcinoma, 52(54.7%) developed after hydatidiform mole, 21(22.1%) after abortion, 18(19%) after normal pregnancy and 4 (4.2%) after tubal pregnancy. 93 cases of hydatidiform mole (93%) and 7 cases of abortion (7%) preceded in 100 cases of destructive mole. The 7% of abortions may be due to inaccurate statement by the patients themselves[9].

Only one case of hydatidiform mole progressed to choriocarcinoma via destructive mole proved by autopsy. The rare existence of "choriocarcinoma with chorionic villi" or so-called "villous choriocarcinoma" is still not be settled by our diagnostic criteria mentioned above.

This report was made a special speech at the 70th Annal Metting of the Formosan Medical Association on November 11,

1977 without publication thereafter.

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過去30年（1947～1976）台灣地區破壞性胎塊及絨毛膜癌的追踪研究

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過去 30 年（1947－1976），我們從國立台灣大學病理科（1947－1966），及私立台北醫學院病理科（1967－1976），收集共 809 個妊娠性滋養層疾病的病例。其中包括 518 例水泡性胎塊，126 例破壞性胎塊，142 例絨毛膜癌及 23 例形態學上診斷未明病例。在過去 30 年，分成三個系列，時間由 6 個月至 5 年不等，來追踪研究，而有 91 例破壞性胎塊及 94 例絨毛膜癌的資料可供使用。破壞性胎塊疾病的死亡率在第一系列（1947－1956），第二系列（1957－1966）及第三系列（1967－1976）各爲 6.3％（1/16）、9.7％（6/62）及 15.4％（2/13）；而絨毛膜癌病例的死亡率則依序爲 88.8％（22/25）、55.6％（25/45）、及 50％（12/24）。全體平均死亡率則分別爲：破壞性胎塊 9.9％（9/91）及絨毛膜癌 62.8％（59/94）。第一系列（1947－1956）係純粹外科治療的死亡率；但從 1962 年，Methotrexate 在台灣被合併使用後，絨毛膜癌的死亡率就明顯地減低。第三系列破壞性胎塊死亡率略微增高，可能係由於比其它系列，較少病例的緣故。

第三系列（1967－1976）中，一例破壞性胎塊在其術後以 Methotrexate 化學治療期間死亡。

破壞性胎塊病人年齡分佈方面是屆於 18 歲至 55 歲，而絨毛膜癌則屆於 18 歲至 61 歲。142 個絨毛膜癌病例中，88 個病例（62％）年齡在 30 歲以上，51 個病例（36％）在 30 歲以下。在台灣，絨毛膜癌似乎較常見於 30 歲以上的人。此年齡分佈是大不同於 Novak 及 Seak 的系列。他們的報告，30 歲以下的人多，66％（49 cases/74 cases）[3]。

95 個絨毛膜癌病例中，52 個病例（54..7％）發生在水泡狀胎塊發生後，21 個病例（22.1％）發生於流產後，18 個病例（19％）在正常生產後，有 4 個病例（4.2％）在輸卵管妊娠後。在 100 個破壞性胎塊病例發生前，有 93 個病例（93％）有水泡狀胎塊，而 7 例（7％）是流產。此 7％之流產病例，可能是由於病人自己不正確之陳述。

只有一例經屍體解剖後，證實係由於水泡狀胎塊經由破壞性胎塊進展爲絨毛膜癌。"絨毛膜癌併存絨毛膜絨毛"或"絨毛性絨毛膜癌"稀少存在仍然無法用我們上述的診斷依據來解決。

此報告是 1977 年 11 月 11 日在台灣醫學會第 70 屆年會特別演講中發表，其後並未正式印刷公佈。

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