

A CLINICO-PATHOLOGICAL STUDY OF 187 CASES OF TROPHOBLASTIC TUMOURS IN THE S.A.T. HOSPITAL, TRIVANDRUM

by

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Introduction

Trophoblastic tumours constitute a large number of neoplasms of foetal origin growing in the maternal tissues. These growths thus exemplify the survival of a foreign tissue in the maternal host by mechanisms not yet clearly understood. Hydatidiform mole and the related trophoblastic diseases occur with increased frequency in the Far East. The exact aetiological factors of these tumours in general and the reason for their high incidence in the eastern hemisphere in particular are still unknown. Many efforts to find a specific causative factor have been of no avail. Interest in the biological behaviour of these tumours has gained a new momentum in recent years. The clinical and pathological characteristics of these growths have an important bearing on their prognosis and management. This paper deals with the clinico-pathological observations made on 187 cases of trophoblastic tumours in the S.A.T. Hospi-

tal, Trivandrum, during a period of ten years (1958-1968).

Review of Literature

The first description of hydatidiform mole was made as early as the sixth century A.D. by Aetius of Amida. This was followed by the reports of De Law Motte in 1729 and Smellie in 1754 (both cited by Brews 1963). Virchow described hydatidiform mole as a myxomatous degeneration of the stroma of the chorionic villi, which was refuted by Marchand 1898 (cited by Ober, 1959) who demonstrated that the changes in the villous stroma are degenerative in nature and that the feature of moles that gives them their distinctive pathological and clinical characteristics is attributable to trophoblastic proliferation.

The modern history of choriocarcinoma begins with the work of Marchand, 1895 (as cited by Ober, 1959) who described this malignancy as an epithelial tumour derived exclusively from the trophoblast. Hertig and Sheldon (1947) reviewed 200 cases of hydatidiform mole and devised a six point scale for the classification of moles into dangerous and innocent ones, depending upon the degree of hyperplasia and anaplasia of the

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chorionic epithelium. This classification was later simplified by Hertig and Mansell (1956). Hunt, *et al* (1953) described three degrees of trophoblastic proliferation. A central Registry of chorionepithelioma was established in 1946 in commemoration of Albert F. Mathieu under the chairmanship of Emil Novak, and a conference on "Trophoblast and its tumours" was held under the auspices of the New York Academy of Sciences in October 1958, which highlighted various aspects of these tumours.

Chemotherapy in choriocarcinoma is just over a decade old. Li *et al* (1956) first described the efficacy of methotrexate in choriocarcinoma and chorioadenoma destruens. They further described their experience in 27 cases whose therapeutic response to methotrexate was observed over a period of two and a half years. Since then several reports have appeared in the world literature regarding the value of chemotherapy in choriocarcinoma. In India, Rao (1961) from Madurai, has reported encouraging results of chemotherapy in choriocarcinoma using methotrexate, cyclophosphamide, vinblastine, etc.

Ross *et al* in 1965 have reported the sequential use of methotrexate and Actinomycin D in the treatment of choriocarcinoma and have found complete remission in 37 out of 50 patients. Kaku (1966) has reported favourable effects of methotrexate and other antimetabolites in prophylactic chemotherapy of hydatidiform mole.

Incidence

In the S.A.T. Hospital, Trivandrum, there were 105 cases of hyda-

tidiform mole, 13 cases of invasive mole, 8 cases of chorioadenoma destruens and 61 cases of choriocarcinoma during the ten year period from 1958 to 1968; the total number of deliveries during the same period in this hospital was 42,910. The total number of pregnancies (including abortions, ectopic gestations and hydatidiform moles) was 50,389. The incidence of the various trophoblastic tumours works out to be the following:

1. Hydatidiform mole	1 in 409 deliveries 1 in 480 pregnancies.
2. Invasive mole	1 in 3,301 deliveries and 1 in 3,876 pregnancies.
3. Chorioadenoma destruens	1 in 5,364 deliveries and 1 in 16,298 pregnancies.
4. Chorio-carcinoma	1 in 703 deliveries and 1 in 826 pregnancies.

The incidence of hydatidiform mole in relation to pregnancy has been reported to be 1 in 2,500 in U.S.A. (Novak, 1950), 1 in 2,000 in U.K. (Ian Donald, 1959), 1 in 200 in the Philippines (Acosta-Sison, 1959), 1 in 232 in Japan (Hasegawa, 1959), 1 in 530 in Hongkong (King, 1956). Rao (1961-62) reports the incidence as 1 in 196.

The recorded incidence of choriocarcinoma varies from 1 in 271 (Hasegawa, 1959) in Japan to 1 in 40,000 reported from the U.S.A. In the Philippines the incidence is 1 in 1,382 (Acosta-Sison 1959) pregnancies and in Hongkong the incidence is 1 in 2,708 (King, 1956). Shetty and Bhasker Rao (1961-62) give an incidence of 1 in 2,958 in Madras. Along with the other Far Eastern countries the incidence in Kerala is nearly eight to ten times that observed in Western countries.

The incidence of malignancy in relation to hydatidiform mole rises

steeply with age. This is probably due to the fact that hydatidiform mole usually precedes choriocarcinoma especially in the older age group (Table I).

where the ratio is reversed in favour of malignant tumours. This finding tallies with the fact that hydatidiform mole has a younger age of incidence and is generally found to precede the

TABLE I
Age

Age in years	Hydatidiform mole 105 cases	Invasive mole 13 cases	Chorio-adenoma destruens 8 cases	Chorio-carcinoma 61 cases	Total malignant cases	Relative incidence
Up to 20	20 cases 19%	1 case 8%	Nil	3 cases 5%	4 cases	1 in 5 cases
21 - 30	55 cases 52%	6 cases 46%	2 cases 25%	26 cases 43%	34 cases	1 in 1.6 cases
31 - 40	17 cases 16%	4 cases 31%	3 cases 37.5%	15 cases 25%	22 cases	1 in 0.8 cases
41 - 50	13 cases 12%	2 cases 15%	3 cases 27.5%	15 cases 25%	20 cases	1 in 1.6 cases
51 & above	Nil	Nil	Nil	2 cases 3%	2 cases	—

The figures in Table I are in agreement with the observations made by Shetty and Bhaskar Rao (1961-62) in Madras, who found the incidence of invasive mole higher in the age group above 35. Similarly, high incidence of malignant trophoblastic tumours was observed in Taiwan by Chien-Tien-Hsu *et al* (1964). The reason for this high incidence of malignancy in this age group may be attributed to the early marriage and multiparity common in these countries.

Table II shows that the relative incidence of hydatidiform mole with respect to malignancy is about 3:1 in the primipara which steadily falls with rising parity and is about even around the fourth para. The fall is observed to continue beyond this

occurrence of malignant trophoblastic tumours.

Multiparity is considered as one of the predisposing factors (Acosta-Sison 1960). Bhaskar Rao (1961) found the incidence of hydatidiform mole to be high in the parity group of five and over. In a series of 232 cases, 25% were primiparas and 33% were in the parity group of five and above.

The relative percentage of the different communities seeking admissions to the S.A.T. Hospital are, Hindus 82% Christians 10% and Muslims 8%. Taking this into account there is no significant predilection for hydatidiform mole to any particular community. But the incidence of malignant tumours is highly significant ($P < .01$) among the Christians (Table III).

TABLE II
Order of pregnancy (Gravida)

Gravida	Hydatidiform mole	Invasive mole	Chorioadenoma destruens	Choriocarcinoma	Total malignant
1st	19 cases 18%	1 case 8%	Nil	5 cases 6%	6 cases 7.3%
2nd	18 cases 17%	1 case 8%	Nil	3 cases 5%	4 cases 4.9%
3rd	20 cases 19%	2 cases 15%	Nil	8 cases 13%	10 cases 12.2%
4th	14 cases 13%	1 case 8%	Nil	10 cases 16%	11 cases 13.4%
5th	8 cases 8%	2 cases 8%	1 case 12.5	4 cases 7%	6 cases 7.3%
6th	5 cases 5%	3 cases 23%	1 case 12.5	6 cases 10%	10 cases 12.2%
7th	3 cases 5%	1 case 8%	2 cases 25%	2 cases 3%	5 cases 6%
8th	5 cases 5%	1 case 8%	1 case 12.5%	7 cases 11%	9 cases 11%
9th	5 cases 5%	1 case 8%	Nil	7 cases 11%	8 cases 9.8%
10th	1 case 1%	1 case 8%	1 case 12.5%	5 cases 6%	7 cases 8.5%
10 +	7 cases 7%	Nil	2 cases 25%	4 cases 7%	6 cases 7.3%

TABLE III
Community-wise distribution of trophoblastic tumours

	Hydatidiform mole	Invasive mole	Chorioadenoma destruens	Choriocarcinoma	Total malignant
Hindus	*(86.1) 81 cases 77%	12 cases 93%	4 cases 50%	40 cases 66%	*(67.2) 56 cases 68%
Christians	*(10.5) 10 cases 9%	Nil	2 cases 25%	17 cases 28%	*(8.2) 19 cases 23%
Muslims	*(8.4) 14 cases 13%	1 case 7%	2 cases 25%	4 cases 6%	7 cases 9%

*Numbers within brackets are the expected values according to hospital admissions.

In 44% of the cases of hydatidiform mole the uterus was enlarged to 20 weeks of gestation or more (Table IV).

TABLE IV

Height of the fundus in 105 cases of hydatidiform mole

Up to 10 weeks	14 cases	13%
11 — 20 weeks	45 cases	43%
21 — 30 weeks	41 cases	39%
31 — 40 weeks	5 cases	5%

In 105 cases of hydatidiform mole, 91 cases (87%) had dilatation and evacuation followed later by a curettage, 1 case had hysterotomy (0.99), 13 cases (12%) had hysterectomy and 24 cases (23%) prophylactic chemotherapy with methotrexate.

Out of the 13 cases of invasive mole, 2 cases (15%) had dilatation and curettage, 3 cases (23%) had hysterectomy, 6 cases (46%) had chemotherapy with methotrexate and 2 cases (15%) had hysterectomy with chemotherapy. Of the 8 cases of chorioadenoma destruens, 5 cases (62.5%) had hysterectomy and 3 cases (37.5%) had hysterectomy and chemotherapy.

Out of the 13 cases of invasive vesicular mole followed, one patient who was treated with methotrexate has conceived and is now attending the antenatal clinic. Her pregnancy is progressing normally and she is now in the late second trimester.

65% of the cases of choriocarcinoma were preceded by hydatidiform mole, 20% by abortion and 15% by normal pregnancy.

In about 81% of the cases the

symptoms manifested within one year of the last conception. In 10% of the cases the symptoms manifested as late as 3 years after the last conception. In one case, the patient developed bleeding per vaginam 5 years after attaining menopause and choriocarcinoma was diagnosed while investigating the cause of post-menopausal bleeding.

No metastases were found in cases of hydatidiform mole (which is in consistency with the observations of Smalbraak (1957). Hertig and Sheldon (1947), however, have observed 5 cases of pulmonary metastases in a series of 200 cases of hydatidiform mole. In choriocarcinoma, pulmonary metastases were found in 30% of cases in the present series, compared to 55% of cases reported by Novak and Seah (1954). Hertz *et al* have reported pulmonary metastases in 13 out of 19 cases (68%). The sites of metastases in 61 cases of choriocarcinoma are given in Table V.

TABLE V

Metastases in 61 cases of choriocarcinoma

No metastases	34 cases	55.7%
Suburethral nodule	17 cases	28%
Lungs	18 cases	30%
Brain	2 cases	3%
Bladder	1 case	2%

Of the 61 cases of choriocarcinoma, 23 cases (38%) had panhysterectomy, 8 (13%) had chemotherapy with methotrexate alone, 13 (25%) had surgery and chemotherapy, 9 (15%) had surgery and deep x-rays, 5 (8%) had excision of suburethral nodule and no treatment could be

given in 3 cases (5%) as they were moribund on admission.

Sixteen out of 61 cases of choriocarcinoma admitted died in the hospital (26%).

Histopathological examination of 61 cases of choriocarcinoma showed villi in 14 cases (23%) and no villi in 45 cases (74%). The diagnosis in two cases rested on clinical grounds and the morphologic appearances of the tumour. The pathology reports were not available in these two cases. Hence, a definite opinion regarding whether villi were present or absent is not given.

66% of the cases of choriocarcinoma did not turn up for follow-up after they were discharged from the hospital. Hence, no conclusion can be drawn regarding the five-year survival rate of these patients.

Chemotherapy in trophoblastic tumours

Treatment with methotrexate in trophoblastic tumours was started in this hospital in 1965. In the beginning, methotrexate, 0.4 mgm per kilogram body weight, was given orally in divided doses. In patients with choriocarcinoma, the treatment was continued till the biological test of pregnancy (male frog test) remained negative on three consecutive occasions, or till the patient became symptom free. Twenty-three cases of choriocarcinoma were treated with this drug. In 8 cases, as the general condition was poor for any major surgical procedure, methotrexate alone was given and in 15 cases panhysterectomy followed by methotrexate was tried. In these cases there was no primary mortality due to the drug. The deaths were mainly due to

extensive metastases in the brain which seldom respond to chemotherapy, whereas metastases in the lungs and vagina responded well to the cytotoxic drug. Certain toxic symptoms were noticed after the administration of the drug and some of them were really incapacitating to the patient.

With oral methotrexate therapy, lip ulcerations were found in 41.1%, stomatitis in 35.3%, diarrhoea in 51.0%, infection in 35.3%, bleeding from the gums in 23.5%, abdominal pain in 5.9%, and alopecia in 5.9% of cases.

From the year 1967, intramuscular injections of methotrexate, 0.6 mgm per kilogram body weight, in the upper and outer quadrant of the thigh, twice a week for 6 weeks (total of 12 injections) were given (intermittent regime). If the biological or immunological test of pregnancy remained positive, a second course of 12 injections was given after an interval of two weeks. Treatment should be continued till the biological and/or immunological tests of pregnancy remain persistently negative or till there is no evidence of tumour activity anywhere in the body. With this mode of treatment there are practically no toxic symptoms and the patients tolerate the drug better. So far, 3 cases were treated on this regime and all of them are doing well.

Prophylactic Chemotherapy in Hydatidiform Mole

During the period 1965-67, 24 cases of hydatidiform mole were treated with methotrexate, 0.4 mgm per kilogram body weight, orally, in divided cases. The course of treat-

ment lasted for four days. Only one course was given in 20 cases to make the biological test of pregnancy negative. In two cases, two courses had to be given. Two cases died due to drug toxicity, the primary mortality due to the drug being 8.3% in this group. In 65% of the cases there were no toxic symptoms. The results and side effects encountered in cases of hydatidiform mole on prophylactic chemotherapy are given in Table VI.

TABLE VI

Results and side effects in hydatidiform mole cases on prophylactic methotrexate

Number of cases treated	24	23 %
Mortality		8.3%
Lip ulceration		25 %
Stomatitis		15.4%
Diarrhoea		26.9%
Infection		23 %
Bleeding from the gums		3.8%
WBC count below 3000/cmm		3.8%
No symptoms		65 %

Twenty of these cases were followed up for more than a year and they remain symptom free so far. Four of them became pregnant and two of them delivered healthy babies, showing thereby the place of chemotherapy in young women who are desirous of conserving the uterus for future child-bearing. With the intermittent regime, the mortality due to drug toxicity could be avoided, and the toxic symptoms were minimised to a great extent.

Summary

This paper deals with the clinicopathological observations made on 187 cases of trophoblastic tumours admitted to S.A.T. Hospital, Trivandrum, during the ten year period 1958-1968. The incidence of chorio-

carcinoma is approximately 1 in 700 deliveries. The incidence of malignancy in relation to hydatidiform mole rises with age and usually molar pregnancy precedes choriocarcinoma in the older age group. The relationship of age, parity, and the incidence of malignancy in different communities are analysed. The onset of symptoms of choriocarcinoma following the preceding gestation, the sites of metastases, the treatment adopted, the place of prophylactic chemotherapy and the routes of administration of the drug are also discussed. The results are tabulated and percentage incidence calculated.

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