MANAGEMENT AND FOLLOW-UP OF INVASIVE TROPHOBLASTIC LESIONS IN WOMEN

by

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The correct diagnosis and the treatment of invasive trophoblastic lesions still present many problems. Recent advances in anti-cancer chemotherapy have opened a new era in their management and prognosis. The trophoblastic cells being undifferentiated in nature can penetrate into the decidua and myometrium and disseminate to distant parts of the body, and such emboli may occur even in normal pregnancy (Haines 1955). Under some pathological conditions there is excessive proliferation of the chorionic epithelium with increased propensity to invasiveness and malignant transformation. The spectrum of variability between normal chorionic tissue and choriocarcinoma is very wide. As these cells are of foetal origin their implantation in different parts of the body is a type of "homograft", whose proliferation and regression may depend on the immunological reaction of the host as well as its defence mechanism. These facts along with the similarity in the clinical pictures in most of the variants make diagnosis and treatment difficult, and prognosis uncertain. Up to now hysterectomy was the sheet anchor of treatment, with frustrating results (Accosta Sisson 1949). Anti-cancer chemotherapy has now widened the scope of conservative approach, specially in young women where preservation of her reproductive function is desirable. In spite of the advent of these drugs a correct evaluation of the chemotherapeutic agents has not yet been established.

Hertz *et al* (1961) asserted that there has been no difference in the response to chemotherapy with or without hysterectomy. Paranjothy (1965), on the other hand, observes that hysterectomy is an important adjunct to chemotherapy in the treatment of choriocarcinoma.

In this paper an analysis of management of 8 cases of persistent trophoblastic lesions after normal and abnormal pregnancies have been presented with a view to indicate the diagnostic problems and to evaluate the roles of chemotherapy and hysterectomy in the treatment of these diseases.

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Material and Methods

Eight patients have been examined and followed up in the Department of Obstetrics and Gynaecology of the Institute of Post Graduate Medical Education and Research, Calcutta, since 1960. The diagnosis of chorioadenoma destruens or chorionic epithelioma was made by clinical examination, bio-assay of chorionic gonadotrophins, radiological demonstration of metastases, histopothological examination of curettings, and finally by examination of the specimens obtained at hysterectomy and/or autopsy.

Methotrexate was given orally using 15 to 25 mg. daily, and the total dosage in each course varied from 75 to 125 mg. During the therapy close observation was kept by clinical examination; review of the progress of the haematological status was assessed before, during and after the therapy, and, liver and renal function tests were performed. When the drug was used before hysterectomy, exploration of the uterus was done after one course of therapy. In five cases the uterus had to be removed after drug therapy. Postoperative drug therapy was given in seven cases.

Complete remission was considered when clinical, radiological and gonadotrophin titres failed to demonstrate the presence of chorionic lesions. All cases were followed up at monthly intervals for a period of one year, three monthly for the second year, and six monthly during the third year.

Results of study and problems of diagnosis

The following table shows the clinical features of eight cases treated and followed up. (Table I).

The age group of these cases varied from 20 to 30. Three cases occurred after second pregnancy and 1 after the first conception. The invasive lesions occurred 1 to 8 months after the last conception. In 4 cases the preceding pregnancy was an abortion, in 3 cases it was a hydatidiform mole, while in 1 case the invasive lesion occurred after a normal pregnancy. The final diagnosis was as follows: choriocarcinoma — 5 cases, chorioadenoma destruens — 2 cases, syncytial endometritis — 1 case.

Of these 8 cases, 5 are still alive and well.

TABLE I

Analysis of cases

	Name	Age	Parity	Nature of last pregnancy	Interval (months)	Final diagnosis	Remarks
1.	K. G.	30	7+1	Abortion	4	Choriocarcinoma	Alive.
2.	B. M.	20	3+1	H. Mole	2	Perforating mole	Alive.
3.	A. M.	25	2+1	Abortion	4	Choriocarcinoma	Alive.
4.	S. S.	29	2+1	Normal pregnancy (twin)	7	Choriocarcinoma	Dead.
5.	C. R.	23	1+1	Abortion	4	Choriocarcinoma	Dead
6.	U. C.	27	1+1	H. Mole	1	Perforating mole	Alive.
7.	B. S.	30	1+1	Abortion	8	Syncytial endometritis	Alive.
8.	R. B.	20	0+1	H. Mole	8	Choriocarcinoma	Dead.

Problems of diagnosis

The usual means of diagnosis are presented in the Table II. There are many fallacies in all of these findings which have been pointed out by Novak and Sheah (1954), Haines and Taylor (1962) and many other authorities.

TABLE II
Clinical findings

Nature of clinical findings	No. of cases	per cent
Vaginal bleeding	8	100
Enlarged soft uterus	8	100
Presence of lutein cysts	5	62.5
Metastasis in lung with fever and haemoptysis	4	50
High Ch. gonadotrophin titre	8	100
Metastasis in vagina & recurrence	2	25

Methods of Diagnosis

I. *Clinical features:* (a) vaginal bleeding following molar or normal pregnancy and abortion, (b) enlarged bulky soft uterus, (c) presence of lutein cysts, and (d) haemoptysis and other systemic manifestations.

II. Histological evaluation of curettings.

III. Determination of chorionic gonadotrophin in the urine.

IV. Demonstration of metastases.

V. Appearance during hysterectomy.

VI. Termination of the disease.

In this series the following symptoms did arouse the suspicion of persistent trophoblastic lesions but final diagnosis could not be established until histopathological examination of the uteri was done. The three cardinal symptoms, namely vaginal bleeding, enlarged soft uterus and high H.C.G. titre were present in all cases.

Bleeding, following normal pregnancy, abortion and hydatidiform mole may occur in benign conditions like placental polyp, syncytial endometritis and post-molar subinvolution. Case 7 (Table I) is an example where bleeding persisted for seven months following an abortion. The chorionic gonadotrophin titre was also high. Histopathological examination of subsequent curetted material established it to be a case of syncytial endometritis.

Haemoptysis, irregular fever and cachexia after normal and abnormal pregnancies may be due to other incidental causes. The well known triad of H.B.E.S. presented by Accosta Sisson (1951) may be found in benign conditions like perforative mole (case Nos. 2 and 6) or syncytial endometritis (Case 7).

Curettings and exploration of uterus have their limitations. Failure to demonstrate chorionic cells may miss the diagnosis of an intramural growth.

According to Haines and Taylor (1962) the lack of orientation in the portion of endometrium and myometrium in curettings make it extremely difficult to judge the limits of infiltration with certainty. Cell proliferation may vary and is not a useful guide in evaluating the degree

of malignancy. In case 3, curettage was performed 4 times for persistent bleeding and in case 2, abdominal curettage during hysterotomy followed by another curetting after one month, failed to give a conclusive diagnosis. A similar result was obtained in case 8 where 3 successive currettages were of no avail as no chorionic cells could be demonstrated. Further, repeated exploration may lead to perforation and dissemination of the growth.

Chorionic hormone titre is not diagnostic whether the values are high, low or zero. Single estimation can be unreliable. Estimations have been known to be negative in very anaplastic cases.

Demonstration of metastases, both pulmonary and vaginal, have been known to regress spontaneously soon after hysterectomy (Case 1). Pulmonary metastases often produces confusion. Case 4 was being treated as pulmonary tuberculosis (Fig. 1). Spontaneous regression of a primary growth and its metastases have been reported by (Park and Lees 1950, Browne 1958). In all these cases there is the likelihood of confusion in final diagnosis between chorionic carcinoma and other benign trophoblastic lesions with metastases.

Examination of the uterus during hysterotomy (Case 2) or hysterectomy does not always help in ascertaining the invasiveness of the chorionic elements (Figs. 2 and 3).

Termination of the disease in death has been said to be the conclusive proof of choriocarcinoma. Regression of both primary and secondary growths have been reported by King (1956). Therefore, it appears that termination of the disease is no proof of the final diagnosis.

Results of Treatment

The result of treatment is shown in Table III. Four cases had one course of pre-operative methotrexate therapy. In 7 cases postoperative therapy was used. Out of these in 4 cases 1 course was necessary, in 1 case 2 courses were given, and in 1 case 5 courses were administered. In this case there was evidence of recurrence after 9 months and 6-mercaptopurin was used in combination with methotrexate. It appears that metastases showed regression in 5 cases and the gonadotrophin titre was appreciably diminished in 4 cases (Fig. 4). The size, the penetrating power

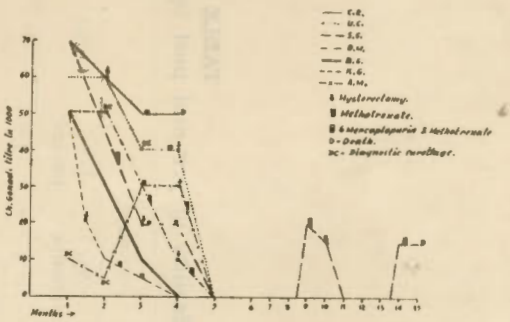

Fig. 4
Graph showing genadotrophin titre before and after chemotherapy and/or surgery.

and the cytological nature of the intrauterine lesion did not show adequate regression after 1 pre-operative course (Figs. 5, 6 and 7). In all these 4 cases hysterectomy and bilateral salpingo-oophorectomy was used as an adjunctive therapy. After hysterectomy 2 cases proved to be choriocarcinoma while the other 2 cases were proved to be chorioadeno-

TABLE III

Results of pre and post operative chemotherapy

Nature of Chemotherapy	No. of courses	Clinical				Radiological			Ch. Gonadothrophin		
		No. of cases	No. change	Improved	Cured	No. change	Improved	Cured	No. change	Improved	Cured
Pre-operative	1	4	3	1	..	..	4	..	..	4	..
Postoperative	1	4	1	..	3	1	..	3	1	..	3
	2	1	..	..	1	..	..	1	..	..	1
	3	..	..	..	..	..	..	..	..	..	..
	4	..	..	..	..	..	..	..	..	..	..
	*5	1—	..	1	..	..	1	..	..	1	..

One case died before institution of therapy.

*Recurrence and death.

ma destruens; symptomatically and clinically they presented identical picture.

Discussion

Many reports have appeared regarding the results of treatment of invasive trophoblastic lesions (Brewer 1961, Hertz et al 1958 Bagshawe 1963) in the last 10 years.

The incidence of spontaneous regression appears to be very low and this has little clinical significance (Bagshawe 1963). The report of 5 years or more survival rate from Albert Mathiew Chorionic Carcinoma Registry in 1961 showed a survival rate of 14.3 per cent out of a total 147 cases where hysterectomy had been used as the only method of treatment.

Lamb *et al* (1964) collected the results reported by different authors after use of chemotherapy; out of a total of 147 cases, 73 (49 per cent) showed complete remission. Though there is general agreement regarding the improvement of results after the advent of chemotherapy certain problems regarding management require critical analysis. These are as follows:

(1) Should anti-cancer drugs be used alone or in combination with surgery? (2) Can the drug forestali the use of hysterectomy in all cases? and (3) What are the chances of successful pregnancy after chemotherapy in metastatic choriocarcinoma?

Brewer *et al* (1964) recently collected the reports of 10 different authors and showed that by use of chemotherapy alone, complete remission was obtained in 35 (54.9 per cent) out of 64 cases. These authors also analysed the reports of 15 other authorities who used chemotherapy along with surgery and complete remission was noted in 54 (48.3 per cent) out of 120 cases. Brewer *et al* (1964) also found that cases with demonstrable metastases responded better to drug therapy alone than when it was combined with surgery. These findings challenge the value of hysterectomy as an adjunctive therapy.

In this series, however, surgery had to be combined, because use of anticancer drugs did not cause adequate regression of the uterine lesions in all cases. Though clinical behaviour, nature of metastases and pattern of chorionic gonadotrophin titre were identical, hysterectomy showed that the final diagnosis was different in almost equal number of cases. It may be that the better results quoted by Brewer *et al* (1964) included some cases of invasive lesions of less malignant character. According to Lamb (1964) these lesions mainly belong to the following groups:

(1) Relatively benign lesions with persistence of raised H.C.G. titre.

(2) Relatively benign lesions with demonstrable metastases.

(3) Chorioadenoma destruens with metastatic lesions.

It seems therefore that chemotherapy should be used in all cases of invasive trophoblastic lesions as an initial method of treatment. Routine removal of the uterus is not justified specially if there is adequate evidence of regression of the tumours. Hysterectomy should, however be performed where after adequate chemotherapy the following conditions are observed:

(a) Regression of primary or secondary lesions are not appreciable, (b) there is evidence of drug resistance, (c) if true chorionepithelioma with metastases is suspected, and, (d) if one has to finally establish the diagnosis of choriocarcinoma.

Pregnancy was not noted in any case of true chorionepithelioma in this series. Freedman *et al* (1962) reported a case where the diagnosis had been based on the report of the vaginal biopsy. As already discussed such findings leave room for doubt regarding diagnosis of real chorionepithelioma.

Summary and Conclusion

1. Eight cases of persistent trophoblastic lesions who presented almost identical symptoms after normal and abnormal pregnancies have been studied and the results are presented.

2. The wide variations and different grades of malignancy in such diseases have been observed.

3. The problems of diagnosis have been discussed. Histopathological examination of the removed uterus is the only means by which the final diagnosis can be established. Other evidences can only lend suspicion.

4. Out of five cases of choriocarcinoma discussed in this series, three developed after abortion, one after hydatidiform mole and one after a normal pregnancy. This indicates that post-abortal bleeding has to be dealt with care and suspicion.

5. The results of treatment have been presented and discussed. Three (60%) out of five proved cases of choriocarcinoma died. Hysterectomy appears to be necessary in treatment of choriocarcinoma along with anticancer chemotherapy.

6. Critical analysis of these cases leaves room for doubt about the good results obtained by chemotherapy alone in the treatment of choriocarcinoma as reported by some workers where the diagnosis was made from curetted material, or biopsy of the vaginal nodule.

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Figs. on Art Paper IX