PROBLEMS IN MANAGEMENT OF TROPHOBLASTIC NEOPLASIA: ROLE OF SURGERY AS ADJUVANT TO CHEMOTHERAPY

by

ASHA JADHAV,* M.S.
NIVEDITA KULKARNI,** M.D., D.G.O.
and
M. V. KANITKAR,*** M.D.

Introduction

The relative rarity and extremely high mortality of untreated chorionic malignancy necessitates that every case be studied and utilised as an opportunity to learn more regarding diagnosis, evaluation and effective management.

Our purpose is to highlight the difficulties involved in follow up and management and to discuss role of surgery as an adjuvant to chemotherapy.

Procedural Methods

Of foremost importance in the management of patients with trophoblastic disease is the utilisation of a test method for human chorionic gonadotropin (HCG) that is sufficiently sensitive to detect low levels of the hormone. Because of the lack of quantitative methods of HCG assessment and limited number of immunological test facilities, the following plan has been involved for the sake of diagnosis and monitoring the therapeutic regimen with regards to their safety and effectiveness. The diagnosis of trophoblastic malignancy is established, based upon combined pathologic and clinical interpretations. Initial immunological urinary pregnancy test was carried out in 1 : 200 dilutions and in lower serial dilutions in case it was negative. A positive pregnancy test was thus taken as a suitable guide both for diagnosis and treatment.

Pretreatment evaluation included the review of the history, physical findings, laboratory tests performed prior and during therapy. There were serial HCG determinations by Gravindex slide method as depicted below, hepatic and renal function tests, total and differential leucocytic count, platelet count, repeated chest X-ray and record of body weight.

During the course of treatment urinary pregnancy tests were carried out after each course of chemotherapy till the undiluted urine showed a negative result. Once the test was reported negative subsequent pregnancy tests were carried after concentrating the urine by modified acetone extraction Tamada *et al* (1966). Concentration was carried out serially upto 32 to 64 times. By concentration technique, detection of HCG levels as low as 750 IU/24 hours is possible. Detection of still lower levels of HCG was carried out by uterine weight assay (Delfe, 1941) which could be established for the third case in our series.

Case 1

A 26 years old, gravida 3, anaemic woman presented with persistent irregular vaginal

*Associate Professor in Obstetrics and Gynaecology.
**Reader in Obstetrics and Gynaecology.
***Reader in Pathology.
Dr. V. M. Medical College, Sholapur.

bleeding for 6 weeks following evacuation of a vesicular mole. Vaginal examination revealed bulky uterus and enlarged ovaries. Her haemoglobin level was 7 gm%, urinary pregnancy test was positive in 1 : 200 dilution, chest X-ray showed metastasis.

Histopathological report of uterine curetting was chorioadenoma destruens. Her hepatic and renal function tests were normal.

After 1 unit of fresh blood transfusion, chemotherapy was started with methotrexate 15 mg daily in divided doses (0.4 mg per Kg) but had to be stopped after 24 hours because of severe gastrointestinal symptoms. She tolerated subsequent four courses of methotrexate 15 mg daily for 5 days with 10 days interval in between. In all 3 units of blood transfusions had to be given during the course of therapy. Her gonadotropin excretion levels dropped gradually, pregnancy test of undiluted urine was reported negative after 2nd course of methotrexate and that of urine concentrated to 32 times was reported negative after the fourth course of methotrexate. Urine concentrated to 64 times showed positive pregnancy test. Further treatment could not be carried out as patient developed jaundice, hepatic coma and death followed.

Case 2

A 35 years old, poorly built anaemic woman presented with severe vaginal bleeding from a large metastatic nodule in vagina. Three years prior she had abdominal hysterotomy and tubal ligation for vesicular mole. Uterus and ovaries were normal in size on clinical examination. Her haemoglobin level was 5 gm%. Urinary pregnancy test was positive in 1 : 200 dilution. No other metastatic deposit could be detected on clinical or radiological examination. Histological examination of vaginal nodule confirmed the diagnosis of choriocarcinoma.

After 2 units of blood transfusion, methotrexate was given as 15 mg daily for 5 days. As bleeding and growth persisted, a combination of methotrexate 15 mg and 6—mercaptopurines 400 mg daily for 5 days was given, following which growth disappeared but pregnancy test of undiluted urine remained positive even after 3 such subsequent courses. However, urine in 1 : 100 dilution was reported negative throughout

Because of this occurrance of resistance, Actinomycin-D was added to above regime as 0.5 mg intravenously on alternate day for 4 days. After that pregnancy test on undiluted sample was reported negative but remained positive in urine concentrated to four times. Patient refused further treatment and hospital stay. Her death was reported a month later due to some unknown infection.

Case 3

A 35 year old, gravida 5, averagely built, severely anaemic woman, presenting as continuous vaginal bleeding inspite of curettage was diagnosed as choriocarcinoma on histopathological examination of uterine curettings. Uterus was enlarged to 12 weeks gravid uterus size and both the ovaries were enlarged and cystic. Her haemoglobin level was 5 gm%. There was no sign of metastasis on clinical and radiological examination. Urinary pregnancy test was positive in undiluted sample but was negative in 1 : 200 dilution. Quantitative assessment by mouse uterine weight assay showed the gonadotropin excretion level as 10,000 I.U./24 hours.

Patient underwent hysterectomy immediately after one course of methotrexate of 15 mg daily for 5 days, following which gonadotropin levels dropped to 5000 I.U./24 hours. On 10th postoperative day, second course of methotraxate was repeated. Thereafter, the levels gradually dropped to 2000 I.U./24 hours and then to 800 I.U./24 hours in 3rd and 6th post operative week.

Further follow up was carried out by immunologic pregnancy test on concentrated urine sample. The test was reported negative in 1 in 64 concentration after 3 months of surgery. Further tests remained negative for a follow up period of 1 year.

Discussion

Gestational trophoblastic neoplasms, metastatic and non-metastatic can be eradicated efficiently with available chemotherapeutic agents in a high percentage of cases. Furthermore, the functional integrity of the reproductive tract can be preserved in most instances.

However, it is important to emphasize that chemotherapy has some drawbacks. These drawbacks in no way detract it

from the position as the primary therapeutic modality in this group of diseases. They should be borne in mind during the course of treatment, so that the effectiveness and safety of the regimen can be adequately judged.

This becomes imperative when the need arises to treat these neoplasms in a part of the world where incidence is more and facilities are limited. Thus to devise a plan of management within the present available setup, without compromising the patients' safety, it becomes necessary to consider various aspects of surgery and chemotherapy.

It is needless to say that excellent laboratory facilities are mandatory if therapy is to be optimum and this is the commonest problem faced by many. With the unavailability of Radioimmunoassay and tedious techniques involved in bioassay, one has to depend on commercial pregnancy test as a guide in diagnosis and monitoring the therapy.

Other difficulty encountered in treating this group of patients is the prolonged treatment requiring hospitalization which is often demoralising to the patient. Although the patients are allowed to go home between the courses of therapy, the total duration of treatment may last quite long. This many a times results in loosing patient's co-operation. Besides, prevention of superadded infection during the course of chemotherapy becomes still more difficult in patient's home surroundings.

A probable though not conclusive inference drawn from a comparative study of the cases presented above was that a higher dose and longer duration of chemotherapy was needed when given alone as in contrast to combination of surgery and chemotherapy. As is apparent from case 3, a lesser amount of chemotherapy succeeded in rapid lowering of gonadotropin levels. This, of course, cannot be said emphatically as the initial H.C.G. titres were low. However, it raises an important question as to how far surgery contributes towards lowering the dosage required probably by reducing the tumor cell mass.

Another observation was that fall in gonadotropin levels did continue for quite some time following a course of chemotherapy and this proved a better criterion for deciding the next course and total dose of chemotherapy required as was suggested by Goldstein (1977). This helped in minimising the dosage and duration of therapy.

Lastly, considering the immunological view point, it may be logical to consider the combination of surgery and chemotherapy synergistic. Though the exact role of immune mechanism both in causation and cure of a neoplasia remaining hypothetical, it may well be presumed that larger the tumor mass, greater is the immunodepression. Any therapeutic manoeuvre including surgery that lowers the tumor burden can alter the immune balance in favour of the patient (Morton 1978).

Thus it is worthwhile considering whether a combination of surgery and chemotherapy could be thought of whenever feasible, as mere reduction of duration of treatment will go a long way in facing the problems during the course of therapy.

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