CHORIONEPITHELIOMA

(A Clinical Study of Sixteen Cases)

by

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Hippocrates and Diocles recognised cystic degeneration of chorionic villi, and Marchand contributed to the knowledge of neoplastic origin from trophoblastic epithelium. Cases of chorionepithelioma were reviewed by Teacher, Smallbraak, A. Sisson, Novak and Seah, Hertig and Sheldon, Gordon King. Park and Lees reviewed 516 cases and Hertz *et al* published results of chemotherapy with Methotrexate in 63 tumours (44 chorionepitheliomas).

In India, Pathare, Benwari, DeSa Souza, Parikh and Sitaratna reported cases of chorionepithelioma, K. B. Rao and Shetty described clinico-pathological features of 27 cases, Mathur *et al* reviewed 10 cases and Paranjyothy reported 37 cases from Vellore.

Incidence

The reported incidence was one in 3708 pregnancies (Gordon King), 1 in 1382 (Sisson), 1 in 2958 (K. B. Rao), 1 in 645 (Paranjyothi) and in our series 1 in 764 deliveries. At the Government General Hospital, Kurnool, there were 16 cases of chorionepithelioma during the period 1958-65, whereas the number of deliveries was 12,224, the number of abortions was 1,855 and of hydatid moles 55.

The average age was 29 years compared to 27.7 years at Vellore. The ages of 7 cases were between 20 and 25 years, of 8 cases between 26 and 35 years and of 1 case 45 years. One patient was nulliparous, 2 were primiparae, 9 second to fourth parae and 4 cases over fourth parity.

Symptoms

The interval between the onset of symptoms and the preceding pregnancy was less than 3 months in 5 cases, 4 months to 1 year in 8 cases, 3 to 7½ years in 3 cases. The delay between the onset of symptoms and the diagnosis was within 3 months in 10 cases, 4 to 6 months in 2 cases and one year in 3 cases. There was no significant difference in the duration between the onset of symptoms and the type of preceding pregnancy.

The incidence of symptoms and signs of chorionepithelioma was: bleeding per vaginam with anaemia, the commonest symptom (in 15 cases). In 2 cases of chronic inversion of uterus the symptom was mass per vaginam; haemoptysis, pain in the chest, cough and dyspnoea were noticed in 4 cases associated with pulmonary metastases. Pain in the

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abdomen (8 cases), vomiting (5 cases) irregular fever (9 cases), mass per abdomen and emaciation (7 cases) were found in advanced cases with extra-uterine spread. Ascites, sciatica, dysuria, jaundice were less common.

Diagnosis

Definite diagnosis was made in the series by examination of curettings in 2 cases, by histology (specimen) of the uterus in 6 cases, biopsy of vaginal metastases in 2 cases, by autopsy in 3 cases and by x-ray of the lungs in 3 cases. Before investigation the diagnosis was cancer cervix in 2 cases of inversion uterus, fibroid of the uterus in 3 cases of mass per abdomen, malignant ovarian tumour in 2 cases and intra-peritoneal haemorrhage in 1 case (tubal pregnancy).

Curettage was done in 8 cases, with negative findings in 2 cases, compared to 3 out of 16 in K. B. Rao's series. Biopsy of vaginal nodule was positive in 3 cases. Frog test for chorionic gonadotropins was positive in six cases, negative in 3, and not done in the rest. Radiological examination showed pulmonary lesions in 9 cases, no secondaries in 3 cases and in 4 cases it was not done.

Treatment

In our series, 5 cases had abdominal total hysterectomy (3 with salpingo-oophorectomy) and 3 had vaginal hysterectomy (one with salpingo-oophorectomy). Vaginal hysterectomy was done in 2 cases of inversion of uterus and in one case of severe anaemia with negative frog test but biopsy report of curettings as invasive mole. In one case abdominal hysterectomy was delayed for 10 weeks due to false negative report on curettings in bicornuate uterus. Post-operatively methotrexate therapy was given to 4 cases, of whom 3 were alive and one died after 10 months due to pulmonary metastases; 3 of the 4 live cases had early diagnosis and surgery. A patient with tumour (pelvic) and pulmonary metastases, who was not fit for surgery, was given chemotherapy (75 mgs of methotrexate) without paliation.

Results

Six patients with severe anaemia were not fit for surgery, 3 were in a moribund state on admission and died later; 4 of the 16 cases were alive from 1 to $2\frac{1}{2}$ years after treatment, survival rate of 25%. Two among the 4 cases of hysterectomy with salpingo-oophorectomy died and oophorectomy did not affect the prognosis. One case of abdominal hysterectomy died soon after operation due to shock and anaemia with advanced growth. A second case died after 49 days due to metastases in the liver, lungs and peritoneum, the diagnosis being cellular fibroid by histological examination of the uterus. A third patient died 10 months after operation due to recurrence and metastases in the lungs resistant to methotrexate therapy. One case of vaginal hysterectomy died 3 days after operation due to ~~shock and blood~~ loss. ~~One patient~~ with diffuse peritoneal metastases following tubal pregnancy died 3 days after laparotomy due to in-

testinal obstruction. Four untreated cases died and 2 cases were taken away in a poor condition.

Two cases with chronic inversion of uterus were reported earlier by the author. Case notes of 3 interesting cases are given below:

Case No. 1.

Mrs. Z. aged 45 years, first para, was admitted on 25-5-'65 with complaints of bleeding per vaginam (since one month), pain in abdomen and retention of urine. Bilateral salpingectomy was done on 28th May '65 at laparotomy for pelvic haematocele. There was a mass in the right fornix at the time of discharge on 7-6-'65. On 24-6-'65 she complained of severe pain in the lower abdomen when pelvic haematocele was diagnosed. On 27-7-'65 she was readmitted in the hospital with severe pain in the lower abdomen, constipation, retention of urine and distension of abdomen of 3 days' duration. Examination revealed hard fixed mass in both iliac fossae and in the posterior fornix and blood-stained fluid was aspirated. On 7-8-'65 emergency laparotomy was done for acute vomiting, pain and distension of abdomen due to intestinal obstruction. There was a diffuse haemorrhagic, friable mass in the abdomen causing low bowel obstruction and chorion-epithelioma was suspected; she died on 11-8-'65. X-ray of chest, biologic test for pregnancy were not done. Histological report of tissue of intraperitoneal growth was chorion-epithelioma. Histology of right tubal pregnancy with rupture of ampullary portion did not reveal malignancy.

Case No. 2.

Mrs. N., aged 30 years, para 2, was admitted on 30-5-'62 with complaint of red and white discharge per vaginam since one year, i.e., 4 months after abortion. Dilatation and curettage was done on 29-8-'61 and 7-9-'61 when she was in the hospital for 6 weeks. On 12-6-62 a mass in the hypogastrium was suspected to be ovarian tumour with pregnancy. Dilatation and curettage was done on 13-7-'62 and the histological report was decidual reaction without trophoblast. Biologic test for pregnancy was positive and x-ray of chest showed hilar opacities, and chorion-epithelioma was suspected on 27-7-'62. On 7-8-'62 total hysterectomy with bilateral salpingo-oophorectomy was done; the left horn of bicornuate uterus was very vascular and enlarged by a tumour (malignant). The pathological report of the tumour was cellular fibroid with red degeneration. On 18-8-'62 there was a mass in the left iliac region and on aspiration blood-stained fluid was obtained. Later irregular fever, swelling and tenderness of left leg, enlargement of liver to 3″ below the costal margin, and pain in epigastrium were noticed. The biological test for pregnancy was positive, 1-200 dilution on 2-6-'62. Post-mortem examination revealed metastases in the lungs, liver and parametrium. The diagnosis was missed due to the negative curettage of the right horn of bicornuate uterus and the misleading pathological report, in spite of positive biological test, bleeding per vaginam, abnormal pelvic mass and history of abortion.

Case No. 3.

Mrs. H., aged 29 years, second para, was admitted on 14-10-'64 with complaint of irregular bleeding per vaginam since 4 months. Her last delivery was 8 years ago and she was investigated for infertility at Hyderabad on 3-8-'62. Dilatation and curettage was done on 10-9-'64 and 19-10-'64 for profuse bleeding per vaginam. The biopsy report was: trophoblastic and decidual cell reaction present. Abdominal hysterectomy was done on 28-10-'64. There was haemorrhagic polypoidal growth arising from the fundus and the pathological report was chorionepithelioma. On 24-10-'64 x-ray of lungs showed no opacities and the biological test for pregnancy was positive. She was discharged on 11-11-'64 and readmitted 8 days later with complaint of haemoptysis. X-ray of lungs showed opacities in the right midzone and left base and pleural effusion on the right side (haemorrhagic fluid).

Methotrexate 15 mg. orally, daily for 5 days, was given from 28-11-'64 and a second course for 5 days from 25-12-'64. The

toxic effects noticed were stomatitis, dysphagia, nausea, vomiting, diarrhoea and pain in abdomen, pruritus, pigmentation of areas of skin and alopecia of scalp. On 18-1-'65 she was discharged relieved and was readmitted six weeks later on 5-3-'65 with haemoptysis and opacities in radiograph of lungs. Methotrexate was given as above from 13-3-'65 and 23-4-'65. X-ray of lungs showed no opacities on 4-4-'65 but a nodule in the right base on 3-5-'65. She was discharged on 30-5-'65 and readmitted on 12-6-'65 with haemoptysis, hiccough and nausea. Fifth course of methotraxate started on 26-6-'65 was complicated by severe toxic effects of vomiting, epigastric pain, giddiness, diarrhoea and stomatitis and had to be discontinued. The liver was enlarged 3 inches below the costal margin; she was taken home on 26-7-'65 and died 5 weeks later i.e. 10 months after hysterectomy. There was remission due to chemotherapy for 5 months and recurrence of pulmonary metastases later was fatal in spite of early diagnosis and radical treatment.

Discussion

Recent reports give a high incidence of hydatidiform mole and chorionepithelioma in the east as compared to that in the west. Interest in these pathological conditions is thus all the greater with us.

In the series presented the type of preceding pregnancy was uterine abortion in 9 cases, hydatidiform mole in two, full-term pregnancy in 4 and tubal pregnancy in 1 case, whereas in K. B. Rao's series the preceding pregnancy was abortion in 11 cases, hydatidiform mole in 11 cases and full-term pregnancy in 5 cases. Two cases of Wei *et al* followed tubal pregnancy and 2 of Sisson's cases followed ovarian and intraligamentary pregnancies, both having malignancy initially. Hertig reported one case of tubal pregnancy with malignant changes which was overlooked at the first examination and later chorionepithelioma was diagnosed.

Metastases were found in the anterior vaginal wall in 5 cases, with oedema of vulva in 2 cases, and pulmonary metastases in 9 cases. The primary growth was in the uterus in 15 cases and in the tube in 1 case, whereas Bhaskar Rao reported 5 cases of metastases in the ovary and in 8 in the vagina. Table shows the comparative incidence of metastases.

The clinical features of H.B.E.S., presence of vaginal or pulmonary metastases, abnormal pelvic mass, positive biologic test for chorionic gonadotropins, were suggested by Sisson as pointers to the diagnosis.

Haemorrhage, necrosis and inflammation along with trophoblasts were believed to be diagnostic "choriocarcinoma triad" by Sutomo (quoted by Sisson).

TABLE I

Site of Metastases

Author	No. of cases	Lungs	Vagina	Parametrium	Ovaries	Peritoneum	Liver
Novak & Seah	74	41	12	5	—	—	—
Park and Lees	516	115	105	19	16	—	—
K. B. Rao	27	10	8	1	5	—	—
Paranjyoti	37	22	13	5	—	—	11
Kurnool	16	9	5	3	—	5	2

Histological, hormonal, radiological and clinical methods are complementary and essential for early diagnosis. Delay was due to failure to have it in mind, non-availability of hormone assays, histology of curettings and false negative reports of intra-mural growths.

In one case repeated curettage of non-pregnant horn of bicornuate uterus did not reveal malignant cells but showed decidual cell reaction and led to delay in the correct diagnosis until operation. In the case of tubal pregnancy followed by chorionepithelioma the diagnosis was missed till laparotomy, as the symptoms and signs were attributed to intra-peritoneal haematoma. One case with haemoptysis was treated in the medical wards for suspected tuberculosis for 5 weeks. In a District Headquarters Hospital, a case of chronic inversion of uterus was kept in for 3 months with suspicion of cancer of cervix, and another case with tumour in the hypogastrium was kept for 4 months without laparotomy. In K. B. Rao's cases, 2 were diagnosed as cancer of cervix, and there was one case of inversion of uterus.

Surgical treatment of chorionepithelioma consists of total hysterectomy and bilateral salpingo-oophorectomy. There is difference of opinion on the necessity or advisability of removal of ovaries, particularly in young women. Treatment of matastases in the vagina is by excision and in the lungs by chemotherapy. Prophylactic chemotherapeutic cover before and after surgery is of recent origin requiring further evaluation. Novak and Seah, Hertz *et al*, Gordon King, A. Sisson, K. B. Rao, Paranjyoty favour removal of the ovaries as a rule in view of the occurrence of metastases and the better long term prognosis, but others like Jeffcoate, Smallbraak, Dilworth and Brews, advocate retention of ovaries in young patients with normal ovaries and doubtful cases of diagnosis prior to hysterectomy. The occurrence of metastases in the ovaries noted by Novak, Paranjyoty and K. B. Rao, has to be weighed against the advantages of oestrogen secretion from the ovaries, the development of immune bodies and inhibition of metastases.

The mortality rate varies in the reported series 70-80% (Novak), 70% (Sisson) 51.5% (K. B. Rao) 94% (Wei *et al*) 80% (Gordon King); in our series 75% of all cases seen and 50% of treated cases.

Chorionepithelioma has poor prognosis due to high degree of malignancy, delay in diagnosis, early wide extension of growth due to blood-borne metastases in distant organs and severe anaemia and cachexia due to profuse blood loss.

In Sisson's cases, 12 of 19 deaths were not so much due to malignancy as failure to recognise the condition early enough to give radical treatment. In our series 8 cases (50%) had no treatment and 8 cases were treated surgically. In case No. 2 (Mrs. N) delay of 10 weeks was due to reliance on curettage despite clinical signs of bleeding, pelvic mass and positive frog test. In case No. 1 (Mrs. Z) as the diagnosis was missed till laparotomy, early treatment could not be given. In our cases the poor prognosis was due to delay in their coming for treatment at a late stage

and lack of enough blood transfusion. Chemotherapy offers better prognosis for palliation in the advanced cases unfit for surgery.

Conclusion and Summary

The clinical features and diagnostic problems of sixteen cases of chorion-epithelioma (one following tubal pregnancy) were studied; the incidence was one in 764 deliveries.

Two cases of chronic inversion of uterus, one of bicornuate uterus with missed diagnosis, one case of diffuse peritoneal metastases following tubal pregnancy and 4 cases treated with methotrexate are in the reported series. Among the factors in prognosis were delay in radical treatment in 3 cases and failure to give treatment in 8 advanced cases. Four cases are alive one to two and half years after treatment and in 3 cases chemotherapy following surgery definitely influenced their chances of recovery and survival. Chemotherapy alone in the advanced cases offers palliation. Early diagnosis and treatment (radical) offer better prognosis, as was the case in 3 of our 4 surviving patients. Post-mortem examination of 3 cases was done which revealed metastases in the lungs, liver, parametrium, vagina, tube and intestine.

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Figs. on Art Paper V