A CASE OF CHORIONIC EPITHELIOMA

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Since chorionic epithelioma is a very rare disease, I would like to report an interesting case of chorionic epithelioma recently seen at the Bombay Hospital.

A female patient aged about 26 years, who was in the third month of pregnancy, went to her private doctor complaining of sudden increase of watery discharge per vaginam. She also reported that she had excessive nausea vomiting during this pregnancy, to such an extent that she was not able to retain anything by mouth since her second month of pregnancy. She was admitted in the private nursing home the same day and was treated on lines of threatened abortion. After about eight days the patient felt a little better and was discharged. Two days later she started bleeding per vaginam which was again treated by a local doctor for a few days. Seeing no improvement in her general condition, she was taken to one of the consultants and was treated in his nursing home. Patient was admitted on 23rd February 1952 with the same history, that is 3 months' amenorrhoea, severe vomiting and bleeding per vaginam for four days. She was a fourth para, and all her previous three were full term normal deliveries—all living. She had her last delivery two years prior to this pregnancy. Her general condition appeared satisfactory except that she was not able to retain anything by mouth. Though the duration of pregnancy was three months, the uterus had grown up to six months' size, reaching almost to two fingers above the umbilicus. There was no ballottament and foetal parts were not palpable at all. The patient also did not feel any foetal movements. The blood pressure and the urine were normal. X-ray of the abdomen was taken but no foetal shadows were visible.

With the provisional diagnosis of vesicular mole it was decided to terminate the pregnancy, and accordingly medical induction was carried out with castor oil, hot douches, hot enemata, mist. ergot, injections of pituitrin, etc. On the 26th February, patient aborted an enormous vesicular mole and it was reported that the vesicles were smaller than usual. Mist. ergot was continued for 4 days and she was discharged on 3rd March, with no blood stained discharge per vaginam.

After she went home she was all right for eight days carrying out all her household activities and enjoying normal health. After eight days she again started bleeding per vaginam which she neglected for two days.

On the third day she suddenly became very ill complaining of severe headache and dowsiness so that she was not able to take interest in the surroundings. She also complained of cough but there was no history of dyspnoea or haemoptysis. Thinking that all these symptoms were due to weakness the private doctor treated her symptomatically for a few days with no improvement at all. As she was going downhill every day, she was sent to Bombay Hospital on 18th March, 1952.

On admission, her general condition was very low and her health had deteriorated to such an extent that she was not even able to sit in bed. She had drowsiness, cough and headache. The B. P. was 100/70 mm. of Hg. and her pulse and respirations were normal. She had no temperature and even though her health was so poor, she could speak and give her whole history in details.

On examination she was found to be emaciated. The lungs were clear except for some rhonchi here and there. The heart was normal though rather weak in action. The central nervous system was not affected, taking into consideration her severe headache and drowsiness. Abdomen was soft and liver or spleen was not palpable at this stage. The uterus was not felt per abdomen.

A vaginal examination revealed a smooth bulky softish retroverted uterus about the size of 2½ months' pregnancy. The cervix was parous and no nodules were felt on it. The parametrium and the fornices were not involved and the ovaries were not enlarged nor were they cystic. Speculum examination did not show any dark or haemorrhagic points in the vagina.

Investigations:

1. Urine—was routinely examined and it was found to be normal.
2. Blood examination—R. B. C. count 2.7 millions. Hb. %—56%.

W. B. C. count	11,500
Diff. W. B. C. count:	
P. M.	68%
Lymphocytes ..	29%
L. M.	2%
Eosinophil ..	1%

3. Urine was sent for Friedman's test and it was reported to be strongly positive. The pathologist reported that even after injection of 1 c.c. of diluted urine in the rabbit (1 in 10) the ovaries were seen actually bursting with the haemorrhagic follicles.
4. The C. S. F. was also sent for chorionic gonadotropin test. The report was not ready at the time of operation but later on it was known that 24 hours rat test with undiluted C. S. F. was positive.
5. X-ray of the lungs was taken and it revealed extensive secondary deposits in both lungs.
6. As she complained of severe headache, some secondaries were also suspected in the brain and so X-ray of the skull was taken which was negative.

With the definite diagnosis of chorionic epithelioma and as the patient was bleeding profusely, she was immediately taken up for operation on 20th March 1952. The abdomen was opened under spinal anaesthesia., Nupercaine 1.5 c.c.

(heavy), by usual subumbilical incision. The uterus was found bulky, pale white in appearance about the size of three months pregnancy. It was quite smooth and no haemorrhagic points were seen on the surface. The parametrium was not involved and the adnexa were not affected to naked eye appearance. They were neither enlarged nor cystic. Taking into consideration the rapidity of the growth, total hysterectomy was performed with removal of ovaries and tubes. All the vessels and the stumps were ligated and the pelvis was peritonised. The liver was palpated but no nodules were felt over its surface. The spleen was also felt normal. The right kidney was found to be little enlarged though no nodules were felt over it. The abdomen was closed as usual.

A blood transfusion of 300 c. c. was given during the operation.

The uterus was cut open after the operation and it showed a small growth about 1" x 2" in diameter with irregular surface, merging into the uterine wall on the posterior wall of the uterus, below the fundus. It was darkish red in colour and with haemorrhagic points at places. There were areas of haemorrhages in the uterine wall. The cervix was not involved.

The post-operative treatment was carried out as usual with prophylactic penicillin injections. Patient had no trouble during the post-operative period, no temperature, and passed urine herself from the day of operation. She was treated with normal haematinics and protein-hydrolysate injections later on.

On the 5th day of the operation—patient developed diplopia and complained that she was not able to see properly. The headache and the drowsiness were same as before. B. P. was 120/80 and urine was normal.

Fundoscopy was done and it showed bilateral papilloedema of the discs and haemorrhages all over the fundus on both sides, suggestive of increased intracranial tension.

Lumbar puncture was done on the 6th day and the fluid came out under tension. It was hazy in appearance and showed blood in deposit. Biochemical examination showed the following features.

Total proteins	55 mg.	per 100 c.c.
Chlorides	730 mg.	per 100 c.c.
Glucose		normal.

Microscopic examination showed occasional R. B. C. and few lymphocytes (3). Bacteriological examination revealed no organisms nor any acid nor alcohol fast bacilli.

On the 7th day of the operation, patient was not able to see any thing and there was no improvement in her general condition. As her headache was getting from bad to worse, she was kept under perfect sedation and spinal fluid was drained out to relieve tension. Her B. P. was 130/80 mm. of Hg.

On the 9th day of operation her B. P. rose to 150/90. In the afternoon she suddenly developed a fit which lasted for two seconds and expired on 28th March 1952 at 2 P.M.

A post-mortem was not available as the relatives refused it. The microscopic report of the section was as follows. The section of the uterine wall shows lining

by normal endometrium with cystically dilated glands. The superficial layer is heavily infiltrated by lymphocytes and few plasma cells—macrophage cells. In the deeper part of the endometrium are seen areas containing organised fibrin. Scattered in these areas are seen few malignant trophoblastic cells. The muscular layer is heavily infiltrated by malignant cells with typical vesicular nuclei showing mitotic figures and protoplasm with irregular and ill defined outlines. These cells are also seen as emboli in the lumen. There is no presence of villi in the whole of the section.

Diagnosis: Chorio-Epithelioma.

Comments. The history and the clinical manifestations were typical of chorionic epithelioma. The patient was under medical treatment right from the beginning and every possible treatment was given to her. The fact that the patient could not be saved in spite of every possible medical aid shows us the definite limit to our modern medical science. The rapidity with which the growth developed after the vesicular mole and the dissemination of metastases all over the body were striking. Probably there must be something in the nature of the vesicles which determines the malignant transformation of a mole, as in the above case, where it was reported that the vesicles were smaller than usual. Even though there were multiple secondaries, the vulva and the vagina, which are the common sites for metastases, were not affected. Also considering the typical nature of vesicular mole and its transformation into its tragic sequelae, the ovaries were not affected nor were they enlarged. The severe headache and drowsiness gave us a clue of secondary metastases in the brain and it was confirmed later on by further trend of symptoms—like diplopia, loss of vision, rise of blood-pressure, etc. Probably the factors which were responsible for affecting the basal ganglia might have further spread to vital centres and killed the patient. There was no time left for us to deal with the metastases.

Discussion.

The incidence of chorionic epithelioma is 1 in 26,000 of pregnancies, but at the same time, it is highly malignant, the mortality rate being 70 to 80%. It was first recognised by Sanger in 1889. It is a parasitic growth, arising from embryonic chorion. It constitutes a pure epithelial form of trophoblastic malignancy derived from any previous form of pregnancy, the uterus being secondarily involved, by invasion, endothelial response, intravascular permiation and ultimate transport to lungs. The typical chorionic epithelioma should be distinguished from chorioadenoma—the invasive vesicular mole which is only locally invasive but runs a benign course, and never kills the patient. It is this variety of chorioma which gives rise to confusion, and leads to erroneous conclusion of high rate of favourable prognosis. Because of frequent difficulty in microscopic diagnosis in this group of cases, many cases, reported as chorionic epithelioma, have

really been highly proliferative but benign hydatidiform moles. The more abnormal the pregnancy, the more it tends to be followed by chorionic epithelioma. The young gravida between the age of 20 and 30, is more vulnerable to this affection than her older sister. It rarely coincides with pregnancy, but in most cases, it develops immediately afterwards. In chorionic epithelioma, the characteristic gross picture is that of a rapidly growing mass, invading both uterine muscles and blood vessels, leading to haemorrhages, and coagulative necrosis. They grow luxuriantly and undergo necrosis at an early age. Microscopically columns and sheets of trophoblasts are seen penetrating the muscle and blood vessels in a lawless manner interspersed with areas of clotted blood. The attempt to villous formation may be there but often absent altogether. Both Langhans and syncytial cells are involved although one or the other may predominate and the former is believed to be more malignant. Anaplastic cell changes are usually present but they are not as definitive in differentiating benign and malignant growth of the trophoblast as in other cases.

The difference between normal invasive trophoblast and that in chorionic epithelioma lies in two points. The former infiltrates along the tissue spaces singly and it never exerts any destructive or lytic effect on the uterine musculature, which the earlier trophoblast of chorionic epithelioma inflicts upon the maternal structure.

It should also be differentiated from invasive mole wherein the trophoblastic proliferation may be extremely marked but there is presence of well marked villous pattern with sharply demarcated margin between the stroma and trophoblast and these show no evidence of destructive or lytic effects on the uterine mulculature.

In the so called atypical form described by Marchand only the syncytial tissue is concerned. Such cases probably represent usually only a syncytial endometritis characterised by abnormal presistence and excess of syncytial tissue which invades the uterine muscle in the implantation area even in normal pregnancy.

Symptoms of chorionic epithelioma may follow immediately after the evacuation of mole or they may be delayed for two years. Sometimes the first indication may be the appearance of metastases in the lungs, vagina, vulva, brain, liver, kidney etc. The incidence of metastases is—lungs 80%, vagina and vulva 50%, kidney, spleen and ovary 13%, pelvis 10%, brain 5%. Haemoptysis suggests secondary growth in the lungs. Patients may come with symptoms of intraperitoneal haemorrhage after the perforation of growth through the uterus. Though it is a carcinoma arising from chorionic epithelium, in the mode of propagation it closely resembles sarcoma.

There is a distressing delay in diagnosing true chorionic epithelioma, following vesicular mole, and that is why we feel that the disease is essentially incurable. Since, however, the disease is very rare and common, it is imperative that no uterus be needlessly sacrificed merely because of such pregnancy.

Chorionic Gonadotropin Test.

Much importance has been given to this test in the diagnosis of chorionic epithelioma. It usually becomes negative from three to six months after the evacuation of hydatidiform mole and should then remain negative. If it becomes positive again it indicates either new pregnancy or chorionic epithelioma. These tests offer no means of differentiating between the two conditions. They are merely of auxiliary value in this respect—the final differentiation being based upon the clinical and histological studies. It is the syncytial element which is responsible for the positive gonadotropin test. In the tumour which consists only of Langhans cells, even though most malignant, the test may come as weakly positive or negative. Accordingly to Browne this negative reaction is due to a variation in the degree of anaplasia present in the cytotrophoblast. The more anaplastic it is, the less strongly positive the reaction will be. This means the more malignant the growth the weaker will be the reaction. Novak is of opinion that the gonadotropic hormone while produced in excess does not gain access to the maternal circulation because of the extensive necrosis produced by these tumours. Various other explanations have been given for this negative phase in the excretion of gonadotropic hormone following reduction in bulk by curettage, fibrin encapsulation of the tumour, or its separation from the maternal circulation by massive blood clots and thrombosis of maternal blood vessels preventing escape of hormone into the maternal circulation.

Chorionic gonadotropin test with cerebro-spinal fluid has also got definite diagnostic value in cases of chorionic epithelioma as it is negative in normal pregnancy.

Value of Curetting.

Curettage should be avoided as far as possible because sometimes dissemination of metastases is provoked by traumatic instrumentation. There are many pitfalls in the diagnosis from the curettings especially as a certain amount of trophoblastic over-growth may be found even in normal pregnancy. The presence of even considerable trophoblastic proliferation is entirely compatible with benign mole and the presence or absence of such attributes as vascular and myometrial invasion cannot usually be determined from the curettings. So the diagnosis in such cases is hazardous. Finally it should be remembered that in certain proportion of cases chorionic epithelioma develops beneath the surface within the uterine wall where the negative report on the examination of curettings will be misleading.

Changes in the Ovaries.

The ovaries are found to be enlarged and cystic in association with hydatidiform mole and chorionic epithelioma in the ratios of 59% and 9% respectively. There were many who formerly believed that these ovarian changes were actually the cause of hydatidiform mole. But with our increased knowledge of endocrinology, there can be no question

that the reverse is the case. These ovarian changes are not due to excessive chorionic gonadotropic hormone as the human ovary is little influenced by them. They resemble rather those which have been brought about experimentally by anterior pituitary sex hormones, which, in these cases, might have been produced through some activator evoked through abnormal excessive production of chorionic hormone.

Although malignant trophoblast is extremely embryonic in appearance its response to radiation is poor. Occasionally isolated metastases have disappeared when eradicated.

Lately attention has been directed by Kullander to the administration of large daily doses of stillbestrol upto 1000 mgms. which seems to have retarding effect on lung metastasis and chorionic gonadotropic titres though it does not cure chorionic epithelioma.

Chorionic epithelioma rarely coincides clinically with molar pregnancy from which it arises, although occasionally its metastases are evident with three to five weeks following the uterine evacuation as in the above case. Although vesicular moles are the prolific source of chorionic epithelioma, it is impossible to predict accurately which mole will be followed by malignant transformation. The marked discrepancy between the size of the uterus and the duration of amenorrhoea suggests malignant nature. Several quantitative tests of Friedman have been advised as they are both of value in diagnosis and prognosis of these cases. This is however difficult here as rabbits are at times not available.

Remarks.

Chorionic epithelioma is the only neoplasm where the primary tumour may disappear or be unrecognisable in the face of distant metastases. Sometimes spontaneous cure has been recorded in some cases. The earlier belief was that the cure was the result of the shutting off of blood vessels by trophoblastic masses. The probable explanation would lie in some unknown factor or general body resistance to trophoblastic growth.

Meigs is of the opinion that this spontaneous disappearance of primary tumour may be due to (1) malignant trophoblasts entering the blood vessels at the site without invading the endometrium or myometrium, (ii) malignant transformation of originally benign trophoblastic emboli.

The same explanation will hold good for the disappearance of metastases after the primary growth is removed. The body can deal with trophoblastic islands, as in retrogression of trophoblastic tissue in lungs of most pregnant women, provided they are not liberated continuously from the primary source.

In Park and Lee's analysis of 516 cases of chorionic epithelioma there are no more than 20 cases of claimed retrogression of pulmonary metastases, reported in the whole world literature. These are confirmed both by X-ray findings and biological pregnancy tests. Mazor and Edeiken reported one case of retrogression of

pulmonary metastases following hysterectomy and subsequent extensive irradiation therapy to lungs.

They have explained this disappearance of metastases by lysin theory of Fraenkel, where he demonstrates some lytic substances in the serum of normal pregnant women which are capable of destroying placental tissue. This substance is absent in the serum of patients with chorionic epithelioma. Perhaps after the removal of tumour these patients are capable of developing this lysin which causes retrogressive changes in the metastases.

Teacher and others describe certain histological changes which suggests a choking off of cancer cells by granulation tissue.

Acosta had carried out statistical study of chorionic epithelioma in Philippine General Hospital. Here the incidence of chorionic epithelioma is greater than in any other hospital. The explanation given for this is that these women are more prolific having as many as 19 pregnancies. He discovered the following facts during the course of his statistical study. If pregnancies rapidly succeed one another and terminate in early months, either as abortion or vesicular mole, the development of chorionic epithelioma is favoured. The greatest age incidence of abortion in his series was in the fourth decade—about 54% and the same was true for chorionic epithelioma. The percentage of malignant transformation from hydatidiform mole was much higher, giving an incidence of as much as 16%. The method of diagnosis they used was curettage and A.Z. test.

In the end I am thankful to Col. Wats, the Superintendent of our Hospital, for allowing me to publish this case and helping me during some of the investigations. I would like to thank Dr. B. N. Purandare, under whose care the case was admitted and operated, for giving me the encouragement and suggestions from time to time and reporting this case and for supplying me with the microphotographs of the specimen. My thanks are also due to Dr. Amin, M.D., Pathologist of our Hospital and to Dr. Chitnis, Hon. Opthalmologist in our Hospital for carrying out some of the urgent investigations at my request.