The Journal of Obstetrics and Gynæcology of the British Empire

VOL. XVI. JULY, 1909. No. 1.

Primary Chorionepithelioma of the Ovary *

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THE case of primary chorionepithelioma of the ovary, on which this paper is based, came under my notice over two years ago. I have allowed this time to elapse before reporting it in order to be able to give something of the after-history of the patient, and perhaps I would have waited still longer had not the publication of two very similar cases from Professor Doederlein's Klinik determined me not to delay further.

The patient was a married woman of 25. She was married at the age of 20 and had had three children and one miscarriage between the first and second child. The last child was born in February, 1905, when there was some difficulty at the confinement, the placenta having to be removed by hand. Three weeks afterwards she went into the Infirmary for "white leg." The child was nursed for twelve months, and after weaning menstruation recommenced. The first period was normal, the next one followed three weeks later, and from then there was a continuous slight loss nearly every day, so that the patient could keep no proper count of the occurrence of the periods. At no time was this loss excessive or such as to suggest to her that she might have had a miscarriage. This state of affairs continued till November, when the loss ceased after an attack of influenza with general pains. When she began to get about after this illness, the pains became localised in the left side and lower part of the abdomen and she suffered a good deal from sickness. About a fortnight before Christmas she noticed a tender lump in the left side of the abdomen, and the medical man whom she consulted advised her to come to the hospital. She was admitted to St. Thomas's on December 28, 1906.

On examination, a tender, hard, elastic swelling was found on the left side of the abdomen, reaching up to the level of the

* Read at Obstetrical and Gynæcological Section, Royal Society of Medicine, June 10th, 1909.

umbilicus. On bimanual examination it did not appear to be connected with the uterus, and was thought to be an ovarian cyst with a twisted pedicle.

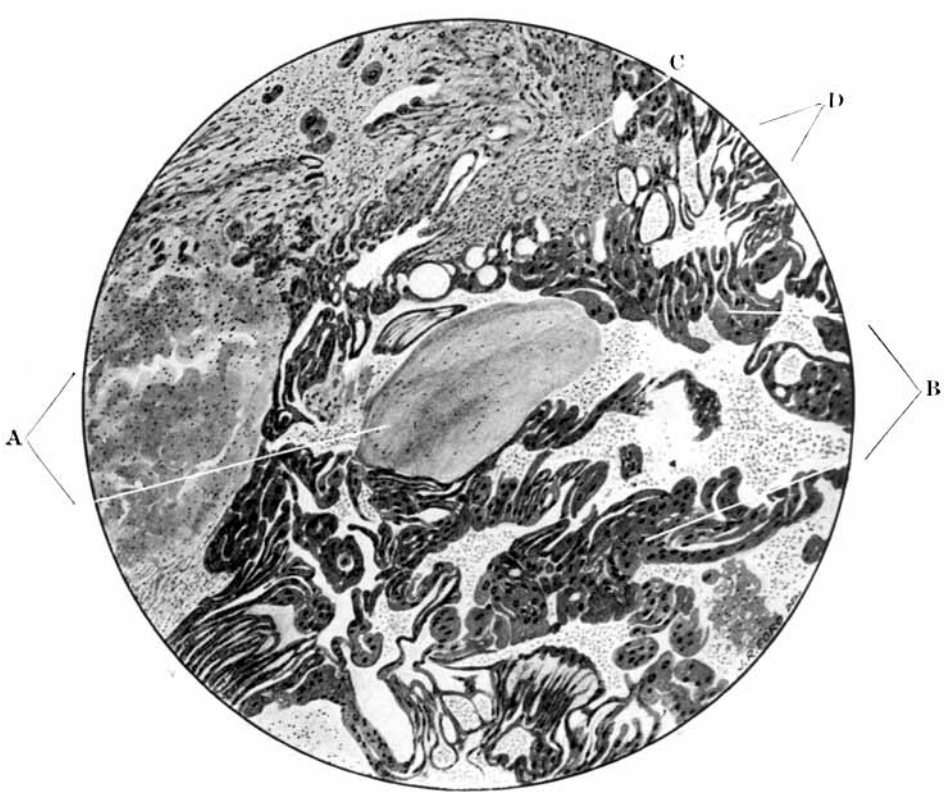
Operation, January 3, 1907. On opening the abdomen, the tumour was seen to be covered with a thin white capsule, through which showed the dark bluish-red colour of the tumour substance. It was very adherent, especially about the level of the pelvic brim, and burst during its separation and allowed of the escape of material so like blood-clot that it at once suggested the possibility of an ectopic pregnancy. When isolated it was found to be a growth of the left ovary but without any twisting of the pedicle. It was removed, and the ovary of the other side also, partly because it was cystic and involved in the adhesions, and partly as a prophylactic measure in view of the evidently malignant character of the primary growth.

The patient made a good recovery, and has remained well up to the present time. She has had complete amenorrhœa since the operation, and except for flushes and heats for a few months, has had no abnormal symptoms. There has been no uterine hæmorrhage or discharge of any kind.

The tumour is of about the size of a small cocoa-nut, measuring $4\frac{1}{2}$ by 3 inches. It is ragged and torn, owing to its having ruptured during removal. The surface is nodular and is covered with the stretched out tunica albuginea of the ovary. The cut edge of the broad ligament can be seen but no trace of the Fallopian tube is recognizable. On section it is seen to be made up of a deep red hæmorrhagic mass, covered with a thin capsule of ovarian tissue. The deep red colour of the cut surface is interspersed with lighter areas, giving it a mottled appearance, and there are fibrous-like strands running through it.

Microscopically the greater part of the tumour is found to be made up of blood-clot, fibrin and necrotic tissue. The chorion-epitheliomatous structure is seen best in portions taken from just under the capsule.

The sections show the remains of the ovarian tissue with follicles and corpora albicantia, and between it and the main mass of clot and fibrin are syncytial masses with small polyhedral cells. The syncytium is especially well developed and forms on the surface of the blood-clot an irregular meshwork of vacuolated protoplasm. There are numerous nuclei of varying shapes, mainly oval or crescentic, and differing considerably in the amount of stain they have taken up. For the most part they have stained deeply. Small compressed masses of polyhedral cells are seen below the syncytium and running in between its strands. Here and there are isolated mononucleated cells. Among the masses of blood-clot are collections of inflammatory leucocytes mainly of the polymorpho-



Section of Growth × 65, showing chorionepitheliomatous structure

A—Blood clot, fibrin and necrotic tissue.
B—Syncytium.
C—Small polyhedral cells.
D—Spaces containing blood.

nuclear type. In this cellular portion there is a large amount of blood, partly clotted and partly free in sinuses between the bands of syncytium. No proper stroma or blood-vessels are present except in the ovarian tissue remaining on the surface of the growth. No traces of teratomatous elements were found in the portions examined.

The case is described as one of primary chorionepithelioma of ovary, and I will therefore begin by noting the points in justification of the title I have adopted.

The naked-eye appearance of the tumour is such as to suggest its chorionepitheliomatous nature, though I will confess that at the time of its removal it did not strike me as such, and that it was not until I had received Dr. Dudgeon's report of the microscopic examination that I recognized how closely the hæmorrhagic structure of the body of the tumour corresponded to the ordinary chorion-epithelioma. Having begun the case from the clinical side and never having had a thought of chorionepithelioma, it is not surprising that the pathological nature of an ovarian tumour of so unusual and unexpected a kind was overlooked in spite of its characteristic appearance. The moment I heard the report from the Clinical Laboratory I could only wonder that no thought of chorionepithelioma had crossed my mind.

The structure of the growth is made perfectly plain by a study of the microscope sections. The syncytial masses, showing marked vacuolation, form a large part of the cellular elements, and with the small polyhedral cells, mononuclear and multinuclear isolated cells, and the huge masses of blood-clot and necrotic tissue, present the typical histological characters of chorionepithelioma.

The other part of the title which has to be justified is the word "primary."

Although the patient had been pregnant four times, there is no history to indicate anything of the nature of a cystic mole or of chorionepithelioma elsewhere. The uterus and vagina were apparently free, and the fact that no other growths have ocurred, though over two years have elapsed since the operation, seems to be sufficient evidence that the growth was one solely and primarily affecting the left ovary. At the same time it is quite evident that the tumour cannot have been of anything like so malignant a nature as is usual with such growths, as it had extensive adhesions to the posterior abdominal wall at the level of the pelvic brim and, being of a soft and friable nature, ruptured during removal so that a certain amount of the clot-like material was extruded into the abdominal cavity, and yet no immediate recurrence took place. It is, however, well known that there are remarkable variations in the malignancy of these tumours. Teacher called attention to this in his valuable monograph on the subject, and mentions that Pick described his first case of primary disease in the vagina as

"*chorionepithelioma benignum.*" Among the favourable cases collected by Teacher, attention may be drawn to that of Cazin-Segond, in which there was a primary focus in the posterior wall of the uterus and a metastasis in the right ovary, and yet the patient was free from recurrence three years after operation. A full discussion of the malignancy and prognosis in tumours of this nature will be found in Teacher's paper.

Several instances of primary chorionepithelioma of the ovary have been described, most of them having arisen in connection with teratomata of that organ. Some years ago Pick collected seven, some cystic and some solid, which he very carefully investigated and described. Michel described a case as one of carcinoma of the ovary, with secondary chorionepitheliomatous deposits in the abdominal cavity, which involved him in a lively controversy with Pick, who maintained that this case was similar to those described by him. Schmaus also recorded a case like that of Michel.

Two papers on primary chorionepithelioma of the ovary have appeared recently, and I have chiefly relied on them for information on the subject. These are an Inaugural Dissertation from Tubingen by Assmuth, and a paper in the *Archiv für Gynäkologie*, 1908 (Bd. lxxxv, p. 415) by Iwase. Both these papers contain the same case from the Tübingen Klinik, but Iwase has a second from the Munich Frauenklinik. Both cases were operated on by Doederlein. Iwase considers that the ovary is by far the most unusual site for extra-uterine chorionepithelioma, and he and Assmuth are agreed in considering that the only case previously recorded which can be considered on all fours with theirs is one of Kleinhans', which possibly may have arisen in a left-sided ovarian pregnancy.

In the first of these cases of Doederlein's, the patient was a woman of 31, who had had two normal confinements and complained of abdominal pain, especially in the right side, and of vaginal hæmorrhage. The last menstrual period had occurred at the beginning of April, 1907, and at the end of May severe hæmorrhage had begun which continued with short intermissions up to the time of her admission to the Klinik on July 17. Three tumours were found in the vaginal wall; the largest, the size of a hen's egg, was just under the urethra, the other two, the size of a hazel nut, were on the posterior wall. The uterus was normal, but to the right was a round, movable tumour, of the size of an apple. The diagnosis of extra-uterine pregnancy was made, the importance of the vaginal tumours being overlooked.

On opening the abdomen a tumour of bluish-red colour was discovered involving the right ovary, of the size of two fists and free from adhesions. This was removed. The left appendages were normal. The vaginal tumours were also removed, the largest one under the urethra being too diffuse to permit of radical extirpation.

Curettage was also done but showed nothing beyond the usual "endometritis glandularis." The vaginal growths rapidly recurred, and the patient was discharged from hospital with signs of metastases in the lungs, and died within a month of the operation. There was no post mortem examination. The section of the tumour showed numerous blood masses between which ran fibrous bands, thus giving it an appearance very like that of the placenta. The vaginal tumours showed a similar structure.

Microscopic examination showed that the main part of the tumour was made up of necrotic tissue and blood fibrin, among which were broken-down tumour cells and blood corpuscles. The structure of the new growth was best seen near the periphery, between the necrotic tissue and the remains of the ovarian tissue. It presented the usual syncytial meshwork with Langhans' cells. Serial sections through the tube gave no sign of tumour elements, and the uterine mucosa removed by curetting showed no evidence of decidual reaction. The nodules from the vagina had a similar structure to that of the main growth.

The second (Munich) case was that of a woman of 42, who was admitted to the University Frauenklinik on October 9, 1907, complaining of severe abdominal pain of six weeks' duration. She had had 11 pregnancies, one of them ending in an abortion at the third month, and in the last two labours the placenta had been adherent and was removed manually. Otherwise there was nothing unusual in her history. Menstruation had been quite regular up to June, 1907, and after then it had ceased. For three weeks before admission there had been a slight loss, amounting only to a few drops of blood.

On examination the uterus was found to the right of the middle line and of the size of a goose's egg; on the left, connected with it and inseparable from it, was a hard tumour the size of a man's head. On October 15, and again on October 17, there was a slight loss of blood. Operation was performed on October 21 by Prof. Doederlein. On opening the abdomen a bluish-black tumour was seen reaching up to the umbilicus. On section it exhibited hæmorrhagic characteristics, which suggested its being a chorionepithelioma following a tubal gestation, and therefore an extensive operation analogous to Wertheim's was done, and the uterus and its appendages with the parametrial tissue and the upper third of the vagina were freely removed. The patient was discharged on November 9.

The tumour of the left ovary was of the size of a child's head, was round, nodular, and of a friable consistence. On section it showed a placenta-like structure. The tube appeared normal. The uterus was somewhat enlarged, but except for an area on the posterior wall, to which the ovarian tumour had been adherent, showed nothing abnormal. The portion of the tumour adherent to it did not involve the uterine wall.

The right ovary contained a small metastatic nodule the size of a hazel-nut and of the same hæmorrhagic structure as the main tumour. The tube of this side also was quite normal. The microscopic examination was much the same as in the first case. The main part of the tumour was made up of masses of blood-clot with necrotic débris, and the cellular portions were made up of syncytial elements and Langhans' cells. The metastasis in the right ovary showed the same structure as the primary tumour. Both tubes were free from tumour elements. The uterus was also free from tumour cells and its mucosa showed no trace of decidual change.

In discussing these two cases Iwase considers the vaginal nodules as secondary metastatic growths in what is the favourite situation for such metastatic growths in the case of chorionepithelioma, but the nodule in the right ovary in the second case he considers as occurring in a very unusual site. In discussing the occurrence of chorionepithelioma outside the area of the implantation of the ovum he mentions three possible explanations. According to Schmorl we may have to do with a case of circumscribed chorionepithelioma or cystic mole, which has been completely extruded from the uterus without leaving any trace in the uterus itself but which, through transportation of the tumour elements, has given rise to a growth at the site where they have settled, so that it appears to be primary.

Pick and others do not consider the previous occurrence of a circumscribed chorionepithelioma or cystic mole as essential, as they consider that the transportation of villi from the normal placenta is sufficient to explain the formation of the growth at the site of transplantation.

The third view is that the tumour may have arisen as a metastasis from a teratoma with chorionepitheliomatous parts. In the case of ovarian chorionepithelioma there are two further possibilities. It may have arisen from an ovarian pregnancy or from a teratoma of the ovary as in the case of similar tumours in the testicle and elsewhere.

Iwase considers that although it is impossible to speak with certainty as to the presence of a teratoma, such is extremely unlikely, as in none of the many sections examined was any sarcomatous or other malignant degeneration found, nor were there any traces of unusual tissue elements. Again, with regard to the possibility of its arising directly from pregnancy, a very careful examination of the genital organs produced no evidence of any changes due to gestation, so that, although menstruation was absent once in the first case and three times in the second case, and in both cases some irregular bleeding accompanied the abdominal pains, too much reliance must not be placed on these clinical symptoms in the absence of microscopical evidence of pregnancy.

The case of Kleinhans, which Assmuth and Iwase consider as the only one like theirs hitherto recorded, was a hæmorrhagic tumour of the left ovary which histologically presented all the signs of chorion-epithelioma. It was partly surrounded by a capsule which contained ovarian tissue. The tubal mucosa was intact but there were some small tumour nodules in the wall. The patient died shortly after the operation, and at the post mortem metastases were found in the lungs and in the vagina. The uterus and the adnexa of the other side were free. Kleinhans was not satisfied that there had been a preceding ovarian pregnancy. The clinical details of this case are not sufficient for the purposes of this paper, and I will therefore confine myself to a consideration of the two cases of Doederlein's, which are extremely interesting as forming a very close parallel with the one I have just recorded. They all occurred in multiparous women in the childbearing period of life (ages 25 to 42), and without any history of a preceding cystic mole. There was some disturbance of the menstrual function, but abdominal pain was the marked symptom in them all. The tumours were similar in their characteristics; not large, of a dark bluish-red colour and encapsuled in the remains of the ovary. The cross section had the same hæmorrhagic appearance, which was compared by Iwase to placenta. Microscopically, they presented the usual characters of chorionepithelioma, and judging from the descriptions of the two other cases the tumour elements were best observed beneath the capsule and between it and the mass of blood-clot and necrotic tissue as described in my case. In none of them was there any evidence of teratomatous structures or of immediately antecedent gestation. In Doederlein's cases there were metastases, in the vagina in one case and in the other ovary in the other, but none in my case. Rapid recurrence followed the operation in Doederlein's first case, and his second case is too recent to speak of definitely; in my case there is no recurrence up to the present.

These cases appear to me to be quite different to those recorded by Pick. Apart from the absence of positive evidence of an origin from teratomatous elements, attention may be directed to the following points of difference.

Among Pick's cases were several among young girls, and on the whole the average age was somewhat lower than in the series quoted above. One patient was 9 years old, and the others 16, 17, 21, 24, 30 and 36 respectively. Except one (the patient of 21) all were nulliparous women. In Michel's case the patient was a young nullipara of 16, with infantile genitalia.

The extremely malignant character of the growth in Pick's cases is shown by the fact that of the six cases in which a record of the result is given, four patients died within a few months of operation, one a year after, and one only is mentioned as being alive for over a year.

The definite evidence of teratomatous structures in these tumours, the more mixed nature of the tumour elements, their occurrence in young girls before the child-bearing age, and in nulliparous women, make it unlikely that the tumour under consideration in this paper, and the two similar ones from Doederlein's Klinik, are of a like origin, quite apart from the fact that no evidence of teratoma is forthcoming.

Further than this any discussion as to the origin of these growths of the ovary must be purely speculative. There is no evidence of a preceding ovarian pregnancy, and considering the rarity of this variety of ectopic gestation, such an explanation would involve the assumption of the occurrence of a very rare sequel of pregnancy on the top of an extremely rare form of pregnancy. In the meantime I would accept Pick's view as to their possible origin from the transported villi of a normal placenta, for the patients in whom these growths occurred were multiparæ and, curiously, in two of them manual removal of the placenta was practised in the labours immediately preceding the commencement of symptoms.

Full references to the literature of the subject will be found in Teacher's monograph (*Journ. of Obstet. and Gynæcol. of the Brit. Emp.*, vol. iv, p. 1) and in the papers mentioned.