Ovarian adenocarcinoma: Metastatic from, or concomitant with, cervical adenosquamous carcinoma?

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A case of bilateral ovarian adenocarcinoma, in which the cervical specimen had a combination of both squamous cell carcinoma and adenocarcinoma is presented. The uterine corpus showed no evidence of involvement. The nature, prognosis and treatment of the cervical lesion and the relation between the ovarian and cervical adenocarcinoma are discussed and the literature is reviewed.

It is generally accepted that squamous cell carcinoma of the cervix arises from the stratified squamous epithelium on the portio vaginalis, and that adenocarcinoma originates on the columnar epithelium within the endocervical canal, although some may be seen to originate on the portio and probably do so in abnormal columnar epithelium of an eversion. However, it is highly likely that there are cells in the cervix, such as basal cells of the columnar epithelium, that may generate both squamous and gland-cell growth, hence the growth can be of a combined type. Johnson et al[1] described lesions in which squamous-cell carcinoma *in situ* developed in fields of subcylindrical cell hyperplasia (reserve-cell metaplasia). These cells may be considered to have the capability of producing either mature gland cells or mature squamous cells. It is possible that they may be able to generate either or both types of malignant neoplastic growth on the cervix. Besides, in the erosion-healing epithelium, we can occasionally find individual cells having mucinous material within the cytoplasm scattered among the squamous type epithelium[2]. Hence the mixed squamous-cell and adenocarcinoma on cervix may have a double primary origin or may be just a single neoplastic process as stated above. Adenoacanthoma is another lesion in which the endocervical adenocarcinoma undergoes squamous metaplasia, possibly resulting from chronic irritation, infection or hormonal influence, but histologically the squamous element is benign.

Glucksmann et al[3] believe that all these tumours can be considered as one group and that the variation in the histological appearance depends on the degree of differentiation. They classify them into three types: (1) mature type (adenoacanthoma); (2) signet-ring cell type, and (3) glassy-cell type. But according to Dougherty & Cotten[2], there are three different arrangements in the relationships between squamous-cell and adenocarcinomatous elements on the cervix. First, the two elements having demonstrably separate origins are termed "mixed or combined carcinomas" – that is, the entirely separate components could be observed in separate locations of the cervix. The second type is a complete merging or mingling of the two elements – that is, the adenocarcinoma is blended with squamous-cell carcinoma, both elements being integral parts of the same growth process. This kind of lesion is referred to as "adenosquamous carcinoma". Of course, the mixed growths of the first type may be seen in some areas, but the finding of merged carcinoma in any part of the lesion is considered to belong to this group. Another arrangement of the two elements in the merged growth is designated as "mucoepidermoid carcinoma". The tumour is typically the squamous-cell variety but containing scattered or clumped cells with intracytoplasmic mucin. The third type is squamous metaplasia of adenocarcinoma. The malignant glandular epithelium transforms into large squamous cells even with pearls or keratin formation. As stated above, the squamous element is benign histologically, and it does not show any atypical change. This type of lesion is termed "adenoacanthoma".

The adenocarcinomatous portion of these growths are of both mucinous and nonmucinous types. The squamous cell carcinomatous component usually consists of undifferentiated cancer. Many investigators have demonstrated a tendency for lesions of adenocarcinoma to metastasize more frequently than squamous cell carcinoma. The results of four representative

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studies on 1,043 patients[4] showed that among 855 with tumours arising on the portio, 24.6 per cent have nodal metastasis. This compared with 38.8 per cent lymph nodes involvement in 188 tumours arising within the canal. Statistically, this difference is significant; it is reasonable to believe that in a lesion of mixed squamous cell and adenocarcinoma on the cervix, the adenocarcinomatous component may be more virulent and may metastasize earlier.

The incidence of such kinds of cervical lesion is unexpectedly higher than generally appreciated, as will be seen if special efforts are made to detect these lesions. Dougherty and Cotten[2] reported 49 cases of mixed squamous cell and adenocarcinoma among 148 instances of endocervical adenocarcinoma, while Wheeless et al[5] gave an incidence of 9.8 per cent. The average incidence as reported at other institutions is around seven to eight per cent[2,3,6].

Pregnancy is associated with carcinoma in 17 per cent of these kinds of lesions[3,6]. The increased incidence in pregnant patients or in those who have had a recent delivery suggests an influence of the hormonal stimulation associated with pregnancy on the type of tumour. The relation might be two fold: (1) the hormonal stimulation might promote a pre-existing carcinogenic process; (2) it might influence the type of differentiation of existing carcinoma cells.

The average age of patients ranged between 40 and 69 years[3,5]. The overall five-year survival for all stages is reported to be 41 per cent[5], which is slightly lower than those of the squamous cell carcinoma of the cervix. Surgical treatment offers a better salvage than radiation. Wheeless et al[5] reported 61 per cent five-year survival rate in patients treated surgically as compared with 45 per cent in patients treated with radiation. There were no survivors in stage III or IV, hence more aggressive radical therapeutic approach as primary treatment of such cancers was highly recommended.

CASE REPORT

The patient (No. 315968 of our hospital), a 51-year-old menopausal housewife, gravida 9 para 9, domicile of Taiwan, was admitted to Mackay Memorial Hospital on June 5, 1973 with chief complaint of recent progressive lower abdominal distension.

She experienced right lower quadrant pain since Feb. 25, 1973. Four days later, she visited a private hospital where acute appendicitis was diagnosed and laparotomy was done on March 1, 1973. A McBurney's incision was used, but actually the appendix was only chronic inflamed. Instead, a foetal head sized ruptured ovarian cyst was found over the right adnexa, which might have been responsible for the abdominal pain. The wound was extended, and the left adnexa was palpated. It was found to be normal. Appendectomy and right partial salpingo-oophorectomy were performed. The specimens were sent for pathological examination and they were reported to be "ovarian papillary adenocarcinoma"(Fig. 1) and chronic appendicitis. She had an uneventful recovery and was discharged after 13

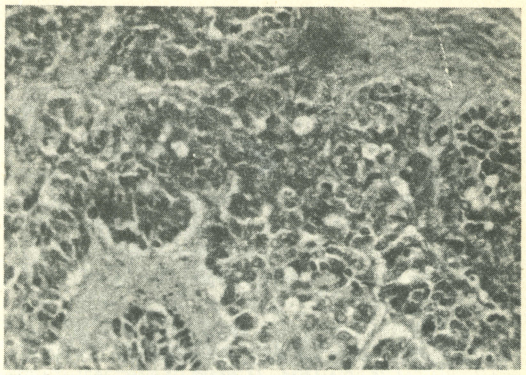

Fig. 1. Papillary adenocarcinoma of right ovary.

days' hospitalization without any further management. Unfortunately, lower abdominal distension gradually developed and became worse as time went on. She visited our hospital and was admitted on June 5, 1973 for further investigation and management. Throughout the whole course of her illness, there were no G-I symptoms nor urinary trouble. She also denied any recent weight loss.

Physical examination on admission revealed a moderately developed obese woman with body weight of 74 kg. The following significant findings were recorded on abdominal and pelvic examinations:

The abdominal girth at navel level measured 120 cm. On palpation, an ill-defined mass was found over the lower abdomen with its upper margin at 3 fb below the umbilical level. No definite signs of ascites were found. The pelvic organs were difficult to outline due to obesity and the tumour mass occupying the lower abdomen. There was resistance on palpation of both adnexa. The cervical portio was only slightly eroded without contact bleeding. The external os was closed with scanty mucoid discharge. Vagina and vulva were normal. Rectal examination was negative.

Laboratory data including haemogram, urinalysis, liver function, renal function, chest PA and EKG all were within normal limits. IVP was taken and showed normal excretory system, except for a pelvic mass shadow. Pap smear was done too, but the result was negative.

Under the impression of "recurrent ovarian carcinoma", exploratory laparotomy was done on June 7, 1973. A big friable mass with an irregular surface, measuring 11 x 8 x 5 cm, was found over the left adnexa, adhering to the parietal peritoneum, pelvic wall, sigmoid colon and left tube. The left infundibulopelvic lig. and broad lig. were also questionably infiltrated. The uterus was slightly enlarged but without direct adhesions to the tumour mass. A scanty amount of brownish coloured ascites was found. "Total hysterectomy and left total salpingo-oophorectomy" were performed smoothly.

On examining the specimen, the uterus measured 11 x 6.5 x 5.5 cm in size; the serosa over the left uterine wall was rough, showing areas of adhesion. On

opening the uterus, an intramural myoma was seen in the right upper fundus; the endocervical canal measured 3.5 cm in length and showed areas of softening. The cervix was eroded. The left ovary measured 8.5 x 5 x 3 cm in size; it was lobulated with adhesion over the external surface. On cut section it was partly cystic, measuring up to 1.8 cm in diameter and partly solid with grayish yellow colour, and soft in consistency. The left tube measured 9.0 cm in length and 1.2 cm in diameter, the lumen was not remarkable but the wall was oedematous and the serosa was coated with thick fibrin-like material.

The specimen was sent for pathological examination. The cervical sections showed foci of adenosquamous carcinoma (Fig. 2), areas of adenocarcinoma

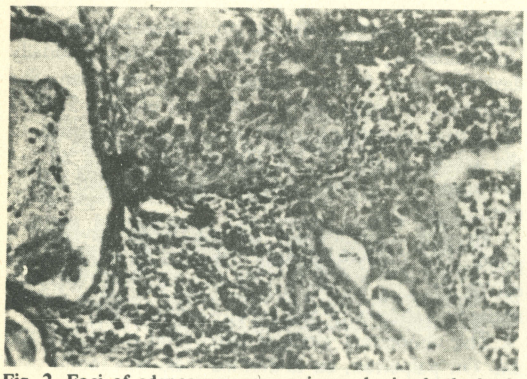

Fig. 2. Foci of adenosquamous carcinoma having both gland-like and squamous-like cells as parts of the same growth; in the right lower field, the lining cells of the glandular space seems half composed of squamous carcinoma cells and half of adeno-carcinomatous components.

with various patterns (Figs. 3,4), and pictures from severe dysplasia to squamous cell carcinoma near the squamo-columnar junction (Figs. 5, 6). The uterine corpus revealed an intramural leiomyoma without any evidence of involvement. The left tube was coated with thick fibrinous exudate with evidence of serosal invasion (Fig. 7). Sections of the left ovary showed patterns of adenocarcinoma with various degrees of differentiation (Figs. 8, 9). Ascites was sent for cytological study, which showed a typical picture of mucous

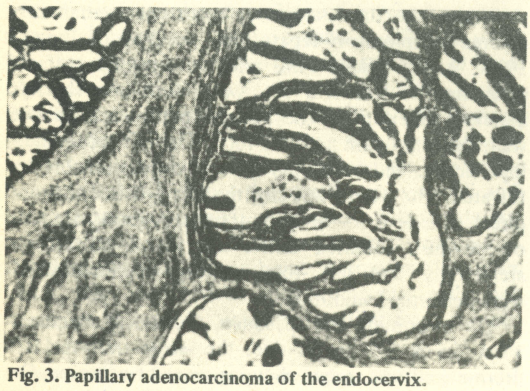

Fig. 3. Papillary adenocarcinoma of the endocervix.

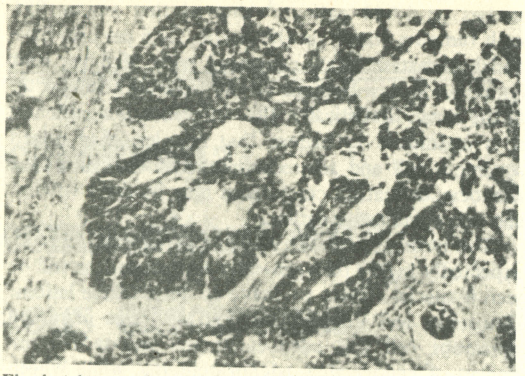

Fig. 4. Adenocarcinoma of the endocervix.

adenocarcinoma (Fig. 10).

The postoperative course was uneventful. The patient was discharged nine days later in good condition. Then she received Co^{60} irradiation from June 18 to July 27, 1973, with a total dose of 6000 rads. After finishing the course, the patient was followed up in our OPD regularly and she was found to be stable in condition. Unfortunately, a sensation of lower abdominal fullness developed again in Oct. 1973. She was admitted on Oct. 22, 1973 and a second look operation was performed two days later. There was no recurrence of

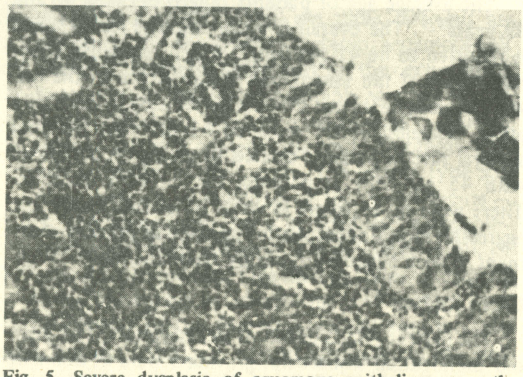

Fig. 5. Severe dysplasia of squamous epithelium near the squamo-columnar junction.

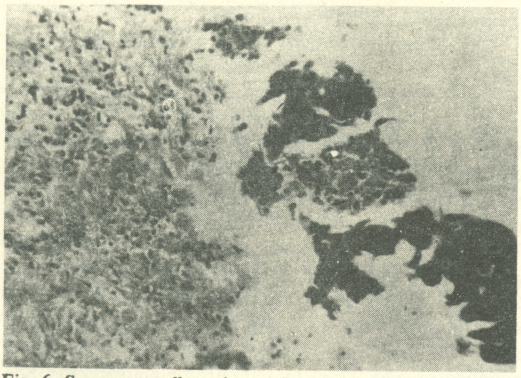

Fig. 6. Squamous cell carcinoma in the neighbourhood of the region shown in Fig. 5.

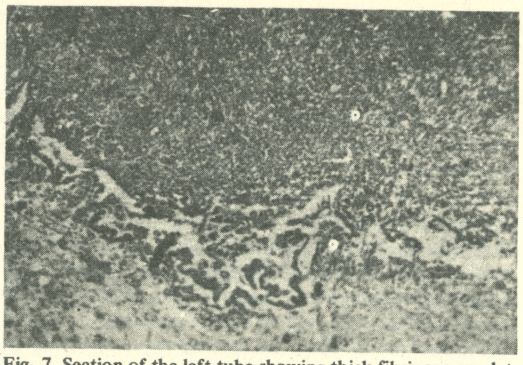

Fig. 7. Section of the left tube showing thick fibrinous exudate coating with evidence of serosal invasion.

tumour growth nor evidence of peritoneal seeding, except that some ascites were found. Endoxan 200 mg was instilled into the peritoneal cavity before closing the abdomen. Ascites for cytology revealed typical mucous adenocarcinoma.

Endoxan injection with total doses 1200 mg, were given before her discharge on Nov. 1, 1973.

Her last visit to our OPD was on Jan. 3, 1974. She was looking rather well, without evidence of any recurrence. Unexpectedly, she was sent to our E-R on Jan. 15, 1974, at 9:30 p.m. due to cardiac-pulmonary arrest. Chest PA taken at a private clinic showed left pleural effusion, and 800 cc bloody fluid was aspirated out by the same doctor. After resuscitation, the patient was declared to have expired at 9:30 p.m.

The total course of events lasted 10 months.

DISCUSSION

Although the incidence of mixed squamous-cell and adenocarcinoma on the cervix is surprisingly high, it is still a rare experience for us to see this kind of lesion. This complex pathological finding brings up many questions.

First of all, we would classify the cervical lesion. On examining the cervical sections carefully we found areas of squamous cell carcinoma blended with adenocarcinoma, as shown in the right lower field of Fig. 2. The lining cells of the glandular space seemed half composed of epidermoid carcinoma cells and half of adeno-

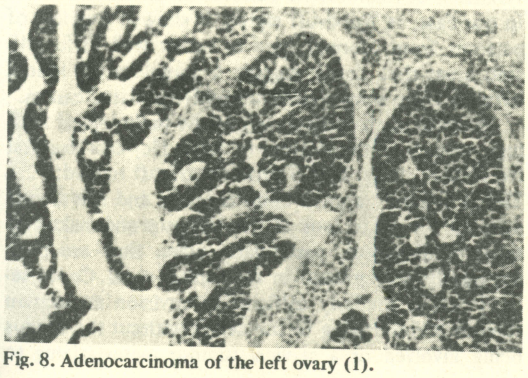

Fig. 8. Adenocarcinoma of the left ovary (1).

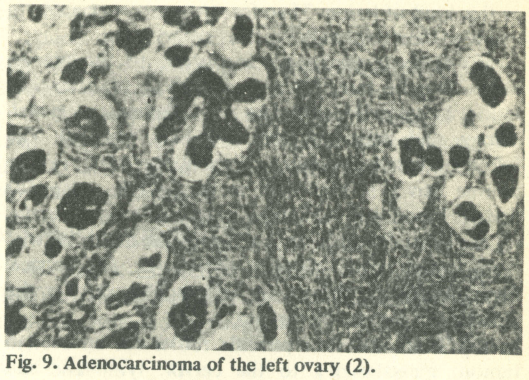

Fig. 9. Adenocarcinoma of the left ovary (2).

carcinomatous components. In these foci of lesions, the squamous cell carcinoma was intermingled with adenocarcinomatous cells. This appearance suggested that the two forms were integral parts of the same neoplastic process; hence, according to Dougherty and Cotten, it should be a type of the adenosquamous carcinoma variety. However, in the sections near the squamo-columnar junction, we found areas of severe dysplasia and a pure picture of squamous cell carcinoma, as shown in Figs. 5 & 6. Deep in the endocervix, the findings were typical adenocarcinoma of various types as shown in Figs. 3 & 4. On first glance, the complete separation of these two components easily led us to the impression of mixed carcinomas. However, it was considered that the finding of intermediate or merged carcinoma in any part indicated that the cancer belonged to the adenosquamous group.

Secondly, the origin of the ovarian adenocarcinoma must be taken into consideration. Did it arise from the ovary primarily? Or did it metastasize from the cervical tumour? Or was it concomitant with cervical lesion as a double primary neoplasm? All these are controversial. Our opinion is that ovarian adenocarcinoma is metastatic from the cervical tumour. The reasons for our conclusion are as follows:

(1) Since the cervical lesion as described above is in favour of the adenosquamous carcinoma group, it means that the cervical lesion is simply a variety of the neoplastic process of one origin. It is less likely that an ovarian tumour metastasizing to the cervix will present

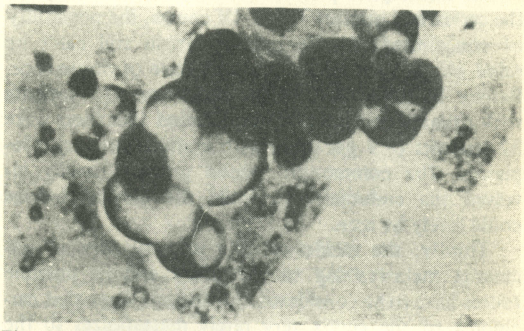

Fig. 10. Ascites for cytology showing a typical picture of mucous adenocarcinoma.

as this kind of lesion. Therefore, it seems reasonable to consider the cervix as being the primary site.

(2) Ovarian carcinoma metastatic to the uterine cervix is quite rare. No note of such an occurrence is found in general textbooks of pathology or gynaecology, and only few cases have been reported. The following conditions may be responsible for it[7]. (a) the uterine cervix is too small to be a target organ; (b) limited blood and lymphatic supply of uterine cervix; (c) the general lymphatic drainage of the uterus is away from, rather than, towards the cervix, (d) cervical fibromuscular stroma is an unfavourable soil for the growth of a metastatic tumour.

(3) There are four possible routes for an ovarian tumour metastasizing to the cervix: lymphatic and haematogenous spread are frequent routes, but the incidence is quite rare as just stated above. Direct extension of the ovarian tumour to the cervix is another possibility, but we found that grossly there was no adhesion between the ovarian tumour and the cervix; and microscopically, the serosa and the deep portion of the cervical stroma were free of involvement. So direct extension is unlikely. In addition to these, the ovarian tumour also can transport the tumour particles through the tubes to the tubal and the uterine mucosa and finally reach the cervix. Serial sections of the uterine corpus showed nothing particular except intramural leiomyoma. No metastatic lesions could be found in tubal or endometrial mucosa. Thus luminal spread also can be ruled out.

Supposing the ovarian tumour is the primary lesion, the most possible route in that case is metastasis by retrograde lymphatic extension to the uterine cervix. Retrograde transport may take place under some pathologic conditions. Eichner and Bove (1954)[4] demonstrated that when the infundibulopelvic ligament was ligated or obstructed by disease, the vital dye which was injected into the hilus of the ovary travelled to the tube via the utero-ovarian ligament towards the uterine corpus, then down the posterolateral aspects of the uterus to the cervix. However, the incidence is extremely rare, especially when the uterine corpus is free from involvement. Therefore, it is unlikely to consider the cervical tumour as a secondary lesion.

From the points discussed above and the similarity of the histological pictures we would like to consider the cervix as a primary lesion. Of course, the possibility of concomitant double primary origin still can't be ruled out in spite of the low incidence of occurrence. Barney B. Silverman[8] in his review on 413 patients with primary ovarian carcinoma found that there were 37 patients (8.9 per cent) with multiple primary neoplasms. The commonest second primary usually involved the endometrium, while the cervical lesions could rarely be seen.

Thirdly, the incidence of a primary cervical carcinoma metastasizing to the ovary and its possible routes have to be considered. All authors agree that carcinoma of the cervix very rarely metastasizes to the ovaries, and certainly much less frequently than carcinoma of the fundus, but it does more frequently than ovarian carcinoma metastasizing to the cervix. Jamil Karsh[9] reported an incidence of 8.8 per cent in 148 patients with cancer of the cervix. However, of the 13 cases, 10 occurred by direct contiguity and only three (two per cent) were metastatic. Among the three, only one (0.7 per cent) was adenocarcinoma. Israel et al[10] reported 3.1 per cent. Woodruff et al[11] in their study of 120 metastatic tumours from the files of the Emil Novak Ovarian Tumour Registry of the American Gynaecological Society gave an incidence of 2.5 per cent. John H. Holzaepfel[12] in his study of 64 treated and 33 non-treated autopsied cases of cervical carcinoma found that the ovaries were involved in seven per cent of the non-treated and in 3.1 per cent of the treated cases. So the incidence is around two to eight per cent.

The method of spread is lymphatic or vascular in the great majority of cases. Direct extension, peritoneal implantation and through tubal lumen occurred in only a few. In our case, there is no evidence of spread via direct extension, peritoneal implantation or even through the tubal lumen as already described. As to the haematogenous spread, Cherry & Glucksmann[4] in their series of 306 cervical cancers, found only 1.6 per cent of clear-cut blood stream invasion, as contrasted with 38.6 per cent with lymphatic embolism. This 24-fold difference is significant. Shaw (1932)[4] also found neoplastic cells metastatic from carcinoma of the cervix in ovarian medullary lymphatics without any detectable blood vessel invasion. So the lymphatic route is the most likely way of spread in our case.

As is known, lymphatic efferents leave the cervix via lateral, anterior, and posterior collecting trunks. Part of them drain into the preaortic and aortic nodes. As the drainage of lymph from the ovary follows the ovarian vessels upward and also terminates in the aortic nodes, so it is possible that cervical carcinoma metastasizes via lymphatics to the aortic nodes and then retrogrades through the ovarian efferent channels to reach the ovary either unilaterally or bilaterally. Bilateral ovarian involvement was reported to be 55 per cent in the Woodruff[11] series and in about two-thirds of the cases in Karsh's study[9].

Metastatic ovarian carcinoma usually shows wide variations of microscopic patterns in the same section. In our case, as Woodruff stated, it showed a variety of patterns from adenoid type to rather well differentiated areas that almost suggest a granulosa cell lesion; between them were masses of undifferentiated cancer.

Because of the complicacy of the pathological findings, we sent all the sections to Johns Hopkins Hospital for further study. Dr J. Donald Woodruff replied: "... This is certainly a most unusual lesion and it is always difficult for me to look at two tumours and make two separate diagnoses, particularly when they are both apparently only present in the genital canal. Conversely, I find it similarly difficult to envision an ovarian tumour metastasizing to the cervix without the fundus being involved or a cervical tumour metastasizing to

the ovary. Both of these situations are rare in my experience. Nevertheless, I must admit that this is a most unusual cervical lesion and seems to arise rather high in the endocervix. I do believe that the cervix is the primary site. I honestly cannot adequately classify it since it has adenoepidermoid, straight adenocarcinoma, and even papillary areas from place to place. It is much more aggressive than the adenoid basal lesions which we have reported in the past. Nevertheless, it does impress me as being an adnexal type of lesion and simulates the various patterns that might be found in a breast cancer. Furthermore, the fact that it has involved the ovary would be rather suggestive of this type of lesion. I do feel that the ovarian lesion is secondary. It shows a variety of patterns from this adenoid type of tumour to rather well differentiated areas that almost suggest a granulosa cell lesion. In between there are large masses of undifferentiated cancer. Consequently, my final diagnosis would have to be a primary adenocarcinoma of the endocervix showing atypical patterns, with metastasis to the ovary. . ."

SUMMARY

This is a case of cervical adenosquamous carcinoma with metastasis to bilateral ovaries via lymphatic spread. The uterine corpus was free from involvement, but the left tube showed evidence of serosal invasion, and ascites for cytology also demonstrated typical mucous adenocarcinoma. However, we could't find any demonstrable evidence to support our diagnosis, so the possibility of concomitant double primary origin still can't be ruled out.

Special stains of cervical and ovarian sections offer little help in determining the site of origin, while histochemical study may be of some value.

The patient had received adequate surgical treatment followed by Co^{60} radiation and expired 10 months later due to cardiac-pulmonary failure with possible lung metastasis.

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