MULTICENTRIC CARCINOMA

A REPORT OF FOUR CASES AND SOME GYNAECOLOGICAL AND SURGICAL ASPECTS

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Malignant disease is an ever-increasing problem in modern medicine. Since the advent of antibiotics, chemotherapeutic agents and hormones, many of the infections and metabolic diseases have been brought under control. Cancer is usually associated with the older age group. Increasing expectation of life thus accounts in some measure for the increasing frequency of malignant disease. When malignant disease attacks the younger age group, it becomes an even greater problem.

Surgery and radiotherapy have been effective in eradicating many early forms of cancer, but the increased life span has brought forth a new hazard—that of new carcinomas originating in other sites. These tumours show no resemblance to the original malignant condition.

Willis,[7] in summarizing the aetiology of multicentric carcinoma, stated that:

> 'The effective stimuli are supplied, not to one cell or one small group of cells, but to a more or less extensive area of epithelial tissue. All the epithelium in that area is acted upon similarly, though of course not equally. Neoplasia will commence where stimuli have been maximal, but the neoplastic response will later be manifested by neighbouring tissue that was subjected to the same original stimulus. The timing and distributing of this progressive response will depend on the distribution and intensity gradients of the causative stimulus.'

There appears to be a 15% chance of developing a second carcinoma,[3] and a 4% chance of developing a third primary growth. Alternatively 15% of all cancers are bifocal in origin, whereas 4% are trifocal in origin. Many patients previously did not survive long enough to develop a second or third cancerous lesion.

In gynaecological practice there appears to be a correlation between carcinomas of the breast and of the female genital organs. It has been found that should a patient with a mammary carcinoma develop a *second new carcinoma* elsewhere, the pelvic genital organs are involved in 40% of these patients.

There is evidence that in some cases therapeutic procedures employed in the treatment of a specific malignant neoplasm, may exert a carcinogenic influence on other organs or tissues. There is also evidence for believing that roentgen therapy or large doses of radioactive isotopes may have a carcinogenic or leukaemogenic effect.

Recently it has been our misfortune to have been associated with 4 such cases.

Short descriptions of these patients follow:

Case 1

Mrs. G.T., aged 33 years, para O, gravida 4, was admitted on 13 May 1963 complaining of a mass in the upper, outer quadrant of the left breast. This mass had been present since January 1963 and was noticed to be progressively enlarging.

In her past history the significant feature was that she had aborted 4 times, this being related to severe cyanotic heart disease, from which the patient suffered. The latter was caused by a Fallot's tetralogy which was later successfully repaired in February 1963.

On examination the general condition was satisfactory. The right breast was normal. The left breast revealed a mass 2 inches in diameter in the upper, outer quadrant which was irregular and quite mobile. There were no palpable axillary glands.

A biopsy by excision was performed. Frozen section showed a poorly differentiated, invasive carcinoma of the breast. A radical mastectomy was then performed. This was followed by a full course of deep X-ray therapy (Fig. 1a).

The patient was also found to have a mass arising out of the pelvis, mainly on the left side. Vaginal examination revealed a normal uterus displaced to the right side by an enlarged, firm, irregular tumour of the left ovary. A smaller ovarian mass could be felt in the right adnexal region.

Laparotomy was performed on 2 July 1963. This revealed bilateral ovarian carcinomas, with secondary deposits above the right kidney, all over the peritoneum and the bowel. Both tumours were removed, and histological examination revealed bilateral papillary serous cyst adenocarcinomata (Fig. 1b).

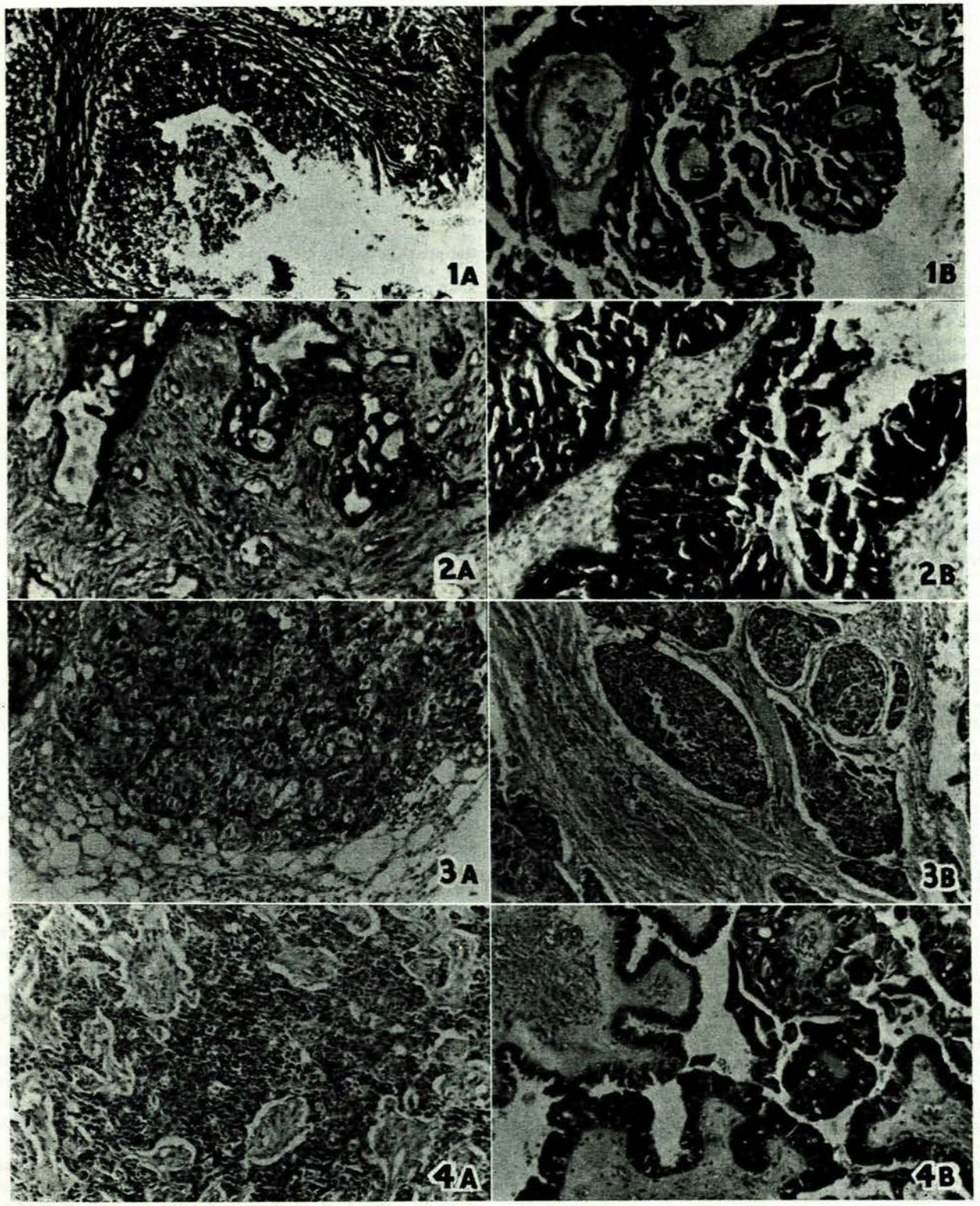

Fig. 1a. A section of the comedo carcinoma of the breast.
Fig. 1b. A section of the papillary serous cyst adenocarcinoma of the breast.
Fig. 2a. A section of the intraduct carcinoma of the breast.
Fig. 2b. A section of the papillary serous cyst adenocarcinoma of the ovary.
Fig. 3a. A section of the skin ulcer showing recurrent breast carcinoma (H. & E. x 90.)
Fig. 3b. A section of the de-differentiated carcinoma of the cervix (H. & E. x 90.)
Fig. 4a. A section of the second breast tumour showing a spheroidal cell alveolar carcinoma of mammary origin.
Fig. 4b. A section of the ovary showing the de-differentiated papillary serous cyst adenocarcinoma (H. & E. x 90.)

Case 2

Mrs. E.R., aged 49 years, para 5, gravida 6, was admitted on 10 September 1963 complaining of swelling of the abdomen for the past month.

In 1952 the patient had a lobectomy for pulmonary tuberculosis, followed by complete remission of the disease. In January 1962 the patient was admitted to the Johannesburg General Hospital with a lump in the left breast.

A biopsy by excision was performed, and frozen section of the tumour showed an intra-duct carcinoma of the breast. A Halsted operation was performed and this was followed by a full course of radiotherapy. Histological examination did not show any further involvement of the breast tissue, although 2 of the 7 lymph glands sectioned showed infiltrating carcinoma (Fig. 2a).

In September 1962 the patient was admitted to the General Hospital, Johannesburg, with a history of excessive vaginal discharge and menorrhagia. A diagnostic dilatation and curettage was performed. The endometrium showed a picture of early cystic glandular hyperplasia. Papanicolaou smears showed no malignant cells. The patient was discharged without further treatment.

On present examination the patient's general condition was satisfactory. A mass equivalent to the size of an 18-weeks pregnancy was found arising from the pelvis. Vaginal examination confirmed the presence of this mass. No other details could be felt.

A laparotomy was performed on 13 September 1963. This revealed a large cyst of the left ovary, and a smaller cyst of the right ovary. Multiple small nodules of carcinomatous tissue were present on the bladder wall, peritoneum and superior aspect of the liver. A total hysterectomy and bilateral salpingo-oöphorectomy was performed. Histology revealed bilateral papillary serous-cyst adenocarcinomata of the ovaries (Fig. 2b). The patient then received a course of deep X-ray therapy.

Case 3

Miss G.P., aged 65 years, para 0, gravida 0, was admitted on 12 September 1963. She complained of vaginal bleeding for 2 weeks. She had menopausal symptoms for the past 15 years.

Past history. In 1956 the patient had a radical mastectomy for carcinoma of the left breast. The patient remained well until 1960 when she developed a recurrence of the carcinoma in the scar of the radical mastectomy, which was treated with radiotherapy.

In May 1963 the patient developed ulceration of the skin of the left axillary region. Biopsy of this skin ulcer revealed a recurrence of the breast carcinoma (Fig. 3a). Radiotherapy was administered to the area, followed by excision of the ulcerated area and skin grafting.

Present general examination revealed that the patient was slightly anaemic and in early, congestive, cardiac failure. The patient was obese and mildly hypertensive (B.P. 190/90 mm. Hg on admission).

Vaginal examination was impossible because of the very narrow, atrophied vagina, but slight vaginal bleeding was noted. Rectal examination revealed a hard fixed tumour in the region of the right adnexa, involving the right pelvic wall. This mass appeared to be the uterus and cervix.

Investigation of the blood showed gross anaemia, hyperpotassaemia, and marked acidosis. X-ray of the pelvis showed a malignant deposit in the left greater trochanter. Cystoscopy revealed complete bilateral ureteric obstruction at the bladder entrance. The bladder itself showed gross induration.

After careful assessment, no therapy was instituted and the patient died from uraemia on 20 September 1963.

Postmortem examination showed a large tumour involving the uterus, ovaries and pelvic wall on the right side. The bladder was also involved in the growth. It apparently originated in the cervix.

Histological examination indicated a markedly de-differentiated squamous carcinoma of the cervix with secondary involvement of the ovary and the lung (sub-pleural region) (Fig. 3b).

Case 4

Mrs. S.P., aged 66 years, para 3, gravida 3, was admitted on 15 March 1963. She complained of discomfort in the lower abdomen. She had menopausal symptoms, dating from 1948.

Past history. In 1943 the patient had a lump removed from the right breast. This was sectioned and found to be carcinoma of the breast. She was treated by radical mastectomy and deep X-ray therapy.

In 1932 the patient had an appendicectomy, and in 1952 a cholecystectomy was performed.

Present examination. The general examination showed nothing of note except the previous mastectomy scar. Abdominal examination showed the previous operation scars. A mass was palpable arising from the pelvis, just to the left of the midline. It was tender and cystic. It corresponded to the size of a gestation of 14 weeks. Vaginal examination confirmed the presence of this mass.

A laparotomy was performed on 25 March 1963. A large amount of blood-stained fluid was found in the peritoneal cavity. A large ovarian cyst was found, replacing the right ovary. The cyst was adherent to the right pelvic wall. A total hysterectomy was performed.

Histological examination showed a de-differentiated papillary serous-cyst adenocarcinoma. The endocervix on section showed a small area of metastatic carcinoma (Fig. 4a).

The patient was treated by a full course of *radiotherapy* to the pelvis, after intraperitoneal radioactive phosphorus had been administered. The patient was discharged on 7 May 1963.

She was *readmitted* on 14 June 1963 with a lump in the left breast. She had complained of pain in the left breast, but no lump had been noted at the time of the previous admission.

A simple mastectomy was performed.

Histological examination showed the presence of a spheroidal cell alveolar carcinoma consistent with derivation from a mammary carcinoma (Fig. 4b).

This illustrates a trifocal carcinoma.

DISCUSSION

In each of the cases described, the carcinoma in the pelvis was completely unrelated to the original breast cancer.

It would be well at this stage to remember the criteria which distinguish a second, primary lesion, from a recurrence or metastatic growth from a primary carcinoma. According to Warren and Gates:[5]

'(*a*) Each of the tumours must present a definite picture of malignancy.
(*b*) Each must be distinct.
(*c*) The probability that one was a metastatic lesion from the other must be excluded.'

In other words it means that each new cancer must be completely distinct from the other and each must show a different histological picture than the original malignancy.

The average interval between first and second cancers was 6·9 years according to Moertal *et al.*[6] (6·4 years in the male, and 7·7 years in the female). The range was from 6 months to 36 years.

The pelvis, it would appear, is associated with neoplasms elsewhere in the body in a significant proportion of cases. Meigs[4] found that 10% of malignancies were associated with carcinoma of the cervix, corpus uteri or ovary. Taussig[2] found that 6·4% of vulvar carcinomas were associated with neoplasms outside the pelvis. It has also been found that 8·3% of ovarian carcinomas were associated with an additional primary carcinoma.[8]

In summary, it appears that the female pelvic organs, particularly the ovaries, are a common site for cancerous growths. The 4 cases described here, as well as evidence in the literature, particularly regarding breast carcinoma and second primary malignancies in the pelvis, makes it essential to review the therapy of breast carcinoma.

It has been advocated by many people that bilateral

oophorectomy should be performed in breast cancer where there has been gland involvement.

In view of the above findings, we should like to suggest that because of the importance of a second primary growth developing in the pelvis, total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed in all cases of breast carcinoma, whether glands are present or not, in those patients past the child-bearing age.

If glands are involved this radical treatment should be employed no matter what the patient's age. If no glands are involved and the woman wishes to have further children, the surgeon would have to 'stay his hand'.

This would appear to be rather radical treatment, but we feel in retrospect that in at least 3 of the patients described, this would definitely have been justified.

Although there is no definite evidence, the ovaries and breasts appear to be under the influence of abnormal oestrogenic activity. This may have a bearing on the high incidence of associated breast and ovarian cancer.

There appears little reason for leaving the uterus and tubes in patients who have had both ovaries removed, particularly in view of the above evidence.

Radiological destruction of the ovaries has no place because of its association with future malignancies. The organs are also still present in the pelvis and may develop secondary malignancies.

SUMMARY

Four cases of multicentric carcinoma are presented with particular reference to the association of breast carcinoma and carcinoma of the female genital organs.

The high incidence of carcinoma of the female genitalia following breast carcinoma is discussed.

Total hysterectomy and bilateral salpingo-oophorectomy are advocated in most cases of breast carcinoma.

It is interesting to note that in all the cases of ovarian carcinoma described, the ovarian pathology was papillary serous-cyst adenocarcinoma.

ADDENDUM

Since this article was prepared a further 8 cases of multicentric carcinoma have been seen by J.A.L.

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