Original Articles

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

REPORT OF A CASE WITH UNUSUAL HISTOLOGICAL FEATURES

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MANY cases of primary carcinoma of the fallopian tube have been reported since Orthmann's first description in 1888, but it is a rare condition accounting for less than 1 per cent of all female genital cancers (Martzloff, 1940). During the period January 1945 to November 1950, 527 cancers of the female genital tract were diagnosed in our laboratory and of the 356 tubes examined, one showed a primary carcinoma which we are discussing in this paper because of its unusual histological features. Since our laboratory undertakes examination of surgical pathological and biopsy material from all but two of the hospitals in Madras State, the figures given above can be regarded as indicating the incidence of the disease in this State. These figures of course do not take into account the proportion of the hospital-going people to the general mass.

Clinical history

A healthy married Hindu female of 50 years, who had had one child, complained of progressively increasing abdominal discomfort, two years after menopause. At operation, the uterus was of normal size, with three small subserosal fibromyomata and the fimbrial end of the right fallopian tube showed an oval, smooth and hard tumour about the size of a fist. The tube and the ovary were removed along with the growth, by resection at the isthmus. Examination during operation revealed no tumour in the uterus, left ovary or fallopian tube. There were no pelvic or abdominal metastases.

Gross specimen

The specimen received consisted of 5 cm. of a slightly tortuous fallopian tube of normal thickness, the fimbrial end of which showed an oval growth 7.75 cm. × 5 cm. × 3.5 cm. (plate I, figure 1). The outer surface of the growth was smooth, opaque white and devoid of adhesions. It had not ruptured anywhere and the abdominal ostium of the tube could not be recognized. A sagittal section through it revealed its friable and papilliferous character, besides hæmorrhage and necrosis (plate I, figure 2). The tubal wall which surrounded the growth completely was 1.5 cm. in thickness at the lower pole where tumour infiltration was noticeable and 0.25 cm. at the upper pole. A probe passed through the tube from the resected end was arrested at the site of the commencement of the growth, where it was markedly constricted and invaginating into the growth. Laying the tube open confirmed this feature and revealed that there was no extension of the growth into other parts. The ovary showed no abnormalities.

Histology

All sections from different parts of the tube, including the resected end and a site 1.5 cm. proximal to the growth, showed features of chronic salpingitis. Mural œdema and diffuse infiltration with lymphocytes, histiocytes and a high proportion of plasma cells were noted. The mucosa was denuded in many parts and consisted of a single layer of deep-staining columnar epithelium in others. None of the sections showed extension of the growth.

Sections from the tumour showed similar chronic inflammation in the surrounding tubal wall which was thinned out in some parts. The most striking feature was the infiltration of the wall, deep into the muscular coat, with sheets of malignant cells showing numerous mitoses but devoid of any pattern (plate I, figure 3). Lymphatic emboli were also seen. The growth itself showed, besides the papillary and papillary alveolar patterns usually described, a highly anaplastic pattern in many areas appearing sarcomatous at first sight (plate I, figures 4 and 5). In the first pattern, the papillæ were covered by as many as nine layers of cuboidal epithelium with deep-staining nuclei and frequent mitoses, the interspaces between papillæ showing inflammatory cells, fibrin and many cells resembling 'peg' cells. In the anaplastic areas the cells were smaller, more spherical and staining more deeply than in others. Mitoses were more numerous and the scanty stroma consisted of delicate connective tissue fibrils.

The ovary which showed corpora albicantes and atretic follicles was free from growth.

Discussion

Wechsler (1926) reviewing the literature on primary carcinoma of the fallopian tube found that 18 per cent of growths occurred about the 50th year and 22 per cent in women who had had only one child. Most of the growths described had arisen from the distal two-thirds of the tube. The case we have described is very similar to these in respect of the age of incidence, parity and site of origin, but presents two rather unusual histological features : (*a*) infiltration of the tubal wall and (*b*) a highly anaplastic pattern, besides the papillary and alveolar ones often described.

Ayre *et al.* (1945) and Novak (1947) said that a striking difference between primary and secondary tubal cancer is the fact that the primary almost never invades the tubal wall, whereas secondary growths almost always invade the tube from without. No explanation has however been given as to why infiltration of the wall does not occur in the former. We feel that although the normal tendency is for the growth to spread along the lumen of the tube into the uterus or into the peritoneal cavity, occlusion of the lumen on either side of the growth, following inflammation, would favour invasion of the wall. It is significant that in this case the tube was constricted and completely occluded just proximal to the growth and the abdominal ostium was not patent.

Primary carcinomas of the tube vary in their degree of differentiation, but most writers have described a papillary and a papillary alveolar type. Novak feels that the papillary type is the only one and that adhesions between the papillary processes produce the alveolar pattern. In this case, many parts of the tumour were highly anaplastic with numerous mitoses simulating a sarcoma. It is possible that this feature was partly responsible for the infiltration of the wall.

Nurnberger, quoted by Robinson (1936) and later Ayre *et al.*, said that the merging of normal columnar epithelium of the endosalpinx with solid masses of neoplastic cells is the criterion needed for the diagnosis of a primary neoplasm. We did not observe normal or hyperplastic epithelium in any of our sections and hence we were unable to see the transition from normal endosalpinx through hyperplasia to malignancy. We feel that this finding is a useful diagnostic aid in early cases, but in advanced ones where the growth has assumed considerable dimensions, it is doubtful if it can be observed.

Excessive œstrogenic stimulation and chronic inflammation are the two factors largely discussed in the ætiology of fallopian tube carcinoma. Proliferation of the uterine glands, squamous metaplasia and neoplasia have been observed in animals following experimental over-œstrinization (Allen and Gardner, 1941) and persistent hyper-œstrinism in the human seems to have a definite rôle in the ætiology of endometrial hyperplasia and cancer. The endosalpinx resembles the endometrium in its cyclic changes and its hyperplasia in response to excessive œstrogenic stimulation is well recognized. As such, it is likely that the rôle of hyperœstrinism in the ætiology of fallopian tube carcinoma and its endometrial counterpart is similar.

The question is often asked why carcinoma of the fallopian tube should be rare in comparison to its endometrial counterpart, if hyper-œstrinism can influence both mucosæ in a similar manner. It is not surprising that it should be so, considering the comparative insignificance of the cyclical changes in the tube, but it is worth noting that the maximal incidence of tumours is in the outer third of the fallopian tube where the mucosa is most plentiful and the cyclical changes more marked than elsewhere.

With reference to chronic inflammation, some regard it as an important predisposing factor, but the great frequency of this lesion in contrast to the rarity of tubal carcinoma would be an argument against this assumption. The changes in the mucosa and the tubal wall in chronic salpingitis are well known, but it is not clear how these favour neoplasia.

We have often observed that where the wall has suffered severe damage from abscess formation and necrosis, during the acute phase of inflammation, pouching occurs in the chronic stage, resulting in what may be regarded as 'micro-diverticula' (plate I, figure 6). It is probable that the epithelium in these regions is exposed to a higher concentration of œstrogens than elsewhere and eventually forms the focus of neoplasia.

We suggest that inflammation and hormonal effects are complementary in the ætiology of carcinoma of the fallopian tube, the former producing structural changes in the organ which favour an intensification of the latter.

Summary

The incidence of primary carcinoma of the fallopian tube, in Madras State, is mentioned.

A case showing an anaplastic histological pattern and unusual infiltration of the tubal wall is described.

Difficulties encountered in the histological diagnosis of the condition and factors favouring mural invasion are discussed.

The rôles of chronic inflammation and hormonal effects in the ætiology of the disease are discussed and a suggestion is made that the former produces structural alteration in the organ which favours an intensification of the latter.

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EXPLANATION OF PLATE I

Fig. 1.—Photograph of specimen. *a*, the tumour, *b*, fallopian tube and *c*, ovary.

Fig. 2.—Photograph of cut surface of tumour. Note its papilliferous character.

Fig. 3.—Photomicrograph of the tubal wall showing infiltration with malignant cells. H. and E. × 160.

Fig. 4.—Photomicrograph from a part of tumour presenting a papillary pattern. H. and E. × 80.

Fig. 5.—Photomicrograph showing an anaplastic area of the tumour. H. and E. × 160.

Fig. 6.—Photomicrograph to show 'pouching' of the tubal wall in chronic salpingitis. *a* and *a'* tubal wall, *b*, mucosa on the pouch. H. and E. × 80.

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MITIGATION OF FLUOROSIS (EXPERIMENTAL)

PART I

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Nature of fluorosis and the need of mitigating it

THE first symptom of chronic fluorine poisoning is the mottled enamel of teeth. When the ingestion of toxic quantities of fluorine extends over a period of 20 to 30 years, the picture of fluorosis in humans 'relates essentially to excessive calcification of ligaments, tendons, fasciæ, the production of osteophytic formations on various bones, almost complete synostosis of the various joints, especially of the vertebral column and nervous effects of mechanical pressure due to encroachment of bone on the spinal cord' (Greenwood, 1940). Relatively little is known definitely regarding the changes that take place in the system during the period intervening between the first symptom of mottled enamel and the final fluorosis of bones. Generally speaking, about fluorine poisoning, one refers either to the mottled enamel of teeth or fluorosis of bones. The first one is caused when water contains more than the permissible quantity of fluorine, *i.e.* 1 p.p.m. The fluorine content of the diet has not been considered so far in regard to the production of mottled enamel. The amounts of fluorine sufficient to produce dental symptoms, nevertheless, may not cause serious bone lesions. The production of bone fluorosis is determined by the quantity of fluorine ingested, the duration and mode of intake, the nutritional status and the age of the subject. The condition of mottled enamel, though much more widely prevalent than the fluorosis of bones, comparatively, cannot be regarded as a serious physiological disorder; whereas, the fluorosis of bones is a major malady causing, besides loss of manpower, untold misery to the cattle and humans. It is very widespread in certain parts of this country and calls for immediate attention and possible solution. In some areas, the suffering due to fluorine poisoning is so great that even if the prevention and cure of bone lesions cannot be accomplished within the near future, the successful reduction of the toxicity of ingested fluorine will have to be regarded as a significant contribution to the solution of this problem. From such a view-point, studies have been carried out in experimental animals by different workers for investigating the possibility of reducing the toxicity of ingested fluorine with dietary and chemical means.

Previous work on the reduction of the toxicity of ingested fluorine with dietary and chemical substances

DeEds (1933) was one of the first to report that dietary calcium reduces the toxicity of ingested fluorine. In the same year, Hauck *et al.* (1933) showed that the growth of rats was poorer on diet containing 0.15 per cent NaF, when the calcium content was low than when it was adequate and that the supplement of vitamin D reduced the toxicity of fluorine in calcium poor diet but not in the calcium rich. Similar observation, regarding the effect of calcium and vitamin D, was, later on, made by Schulz (1938). The protective action of dietary calcium against the toxic action of fluorine has been noted by Lawrenz and Mitchell (1941) and Ranganathan (1941, 1944) in rats, by Velu (1933) in sheep, and by Majumdar and Ray (1946) in bulls. Majumdar and Ray have further reported that the addition of calcium and phosphorus salts in amounts adequate to bring the quantity and the ratio between two minerals to optimum levels helped in protecting the animals for long periods against fluorine intoxication. Pillai *et al.* (1944) have observed that the inclusion of sufficient quantities of whole milk powder in the diet of the experimental rats afforded a remarkable protection against poisoning in the animals. A supplement of bone powder also brought about considerable relief.

Phillips and Chang (1934) observed that 4 cc. or more of orange juice fed with the diet prolonged the survival period of young growing rats fed sodium fluoride in the concentration of 0.2 per cent of the diet. Pandit and Rao (1940) found that the administration of vitamin C lessened the severity of fluorosis in monkeys.

Fargo *et al.* (1933, 1938) in pigs and Evans and Phillips (1939) in rats observed that the simultaneous ingestion of green grass reduced the toxicity of fluorine.

Sharpless (1936) obtained a notable reduction in fluorine toxicosis in rats with aluminium chloride. Majumdar and Ray (1946) also obtained more or less similar results with this substance in bulls.

However, it must be pointed out that in none of these instances has it been reported that

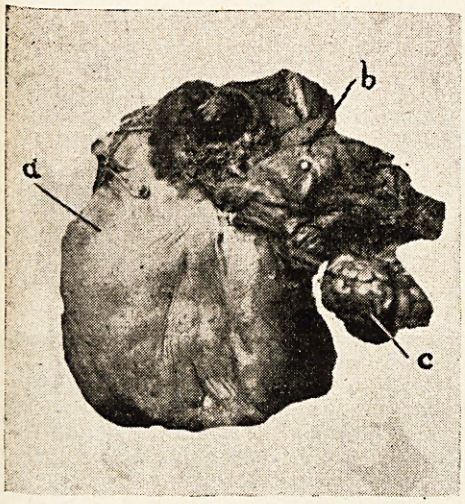

Fig. 1.

Fig. 2.

Fig. 3.

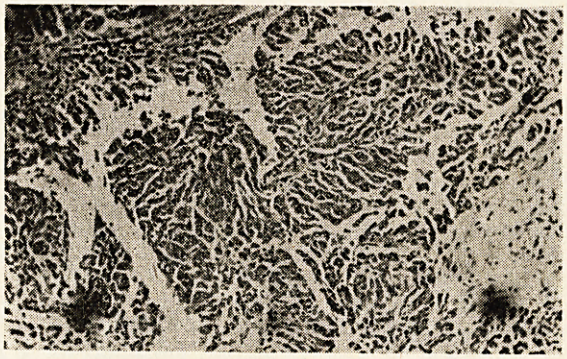

Fig. 4.

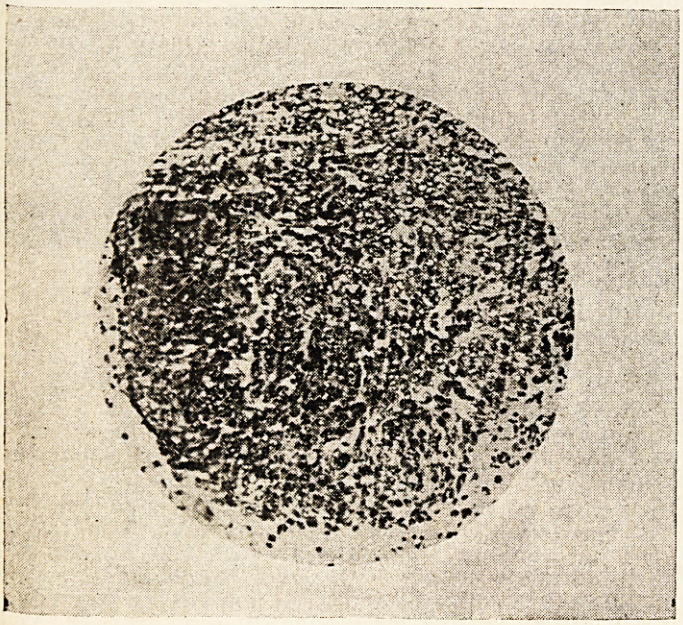

Fig. 5.

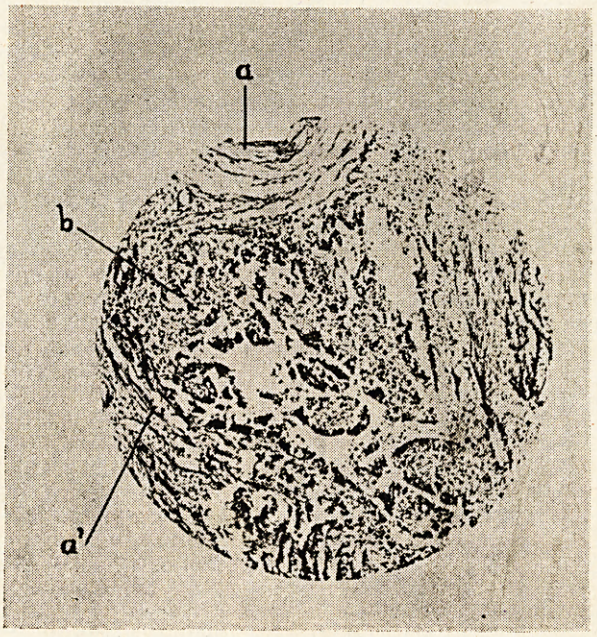

Fig. 6.