

Adenocarcinoma of the Body of the Uterus in Association with Adenomyoma Diffusum Benignum.

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DOUBLE tumours of the uterus are by no means rare. Fibroids and carcinoma are frequently associated, and cases of fibroids and sarcoma, carcinoma and sarcoma, and even of two apparently independent carcinomatous growths have been recorded from time to time. The association of an adenocarcinoma of the corporeal endometrium with a diffuse adenomyoma of the body of the uterus is a much less frequent event. The condition is well exemplified in the following case which we have recently had under our observation.

Clinical History.

The patient is 57 years of age and unmarried. For a matter of 17 years she was the subject of progressive muscular atrophy, which however now seems to be arrested, while about 18 years ago she was operated on for hæmorrhoids. With these exceptions she has never had any really serious ailment.

The present illness began about 8 years ago with increase in the duration of the menstrual periods and in the amount of blood lost on each occasion. The intermenstrual part of each cycle gradually became less and less until about 6½ years ago, when the hæmorrhage became almost continuous. Sometimes the hæmorrhagic discharge ceased, and was replaced by an abundant flow of clear sticky fluid. Two years ago the condition improved considerably, and she was even able to go for two or three weeks at a time without loss of blood. Very often the clear discharge made its appearance a week before the period. During the past year the hæmorrhage has again been excessive, though not continuous, and occasionally the clear discharge has been present. Pain at the menstrual periods began to be very severe about five years ago, but has been less during the past three years. Nevertheless there has generally been a good deal of back-ache and pain in the thighs, always increased at the bleeding times. Slight increase in size of the uterus was first observed two years ago, and the enlargement has been slowly progressive. Six weeks before operation the organ was appreciably enlarged and retroverted.

Mr. Littlewood performed hysterectomy on May 15, 1912, and the patient made an uninterrupted recovery. She has since remained in good health, except that she is rather nervous, and subject to occasional fits of depression and of excitement.

Naked-eye Characters of Specimen.

The uterus is uniformly enlarged to about four or five times its normal size. On section, the muscular wall of the organ is seen to be roughly divisible into two zones, an outer, narrower one of apparently unaltered uterine muscle, and a broad inner one which is dotted throughout with small yellowish areas of soft consistency. Some of the latter show definite cystic change, but all the cysts are of very small size. The endometrium is greatly and irregularly thickened, and presents numerous rounded, boss-like masses filling up the cavity of the organ. It is ill-defined at its junction with the muscular wall. The fungous condition stops short at the os internum, and the cervical endometrium appears normal. The left appendages only are present, and the ovary contains a small cyst the size of a cherry.

Microscopic Characters of Specimen. (a) Myometrium.

The greatly thickened muscular wall of the uterus presents different appearances in its outer and inner parts, corresponding to the differences already noted naked-eye. The outer third presents more or less the normal microscopic characters of the myometrium except that the vascular channels and spaces are perhaps a little more numerous and a little larger than usual. The inner two-thirds present the typical characters of an adenomyoma diffusum, that is to say, there are islets of adenomatous tissue irregularly scattered throughout the unstripped muscle of the uterus. These islets are but few in number, and in a given section they appear to vary greatly in size. Each consists of a collection of glandular acini embedded in a fairly abundant stroma of spindle, round and oval cells, which at the margin merge very gradually into the surrounding unstripped muscle. The glandular acini are lined by columnar ciliated epithelium from one to three layers deep. Most of the acini are about the same size as the normal glands of the endometrium, and indeed closely resemble them in appearance (figure 1), but a few are markedly cystic, giving rise to the cystic appearance in the naked-eye specimen. The epithelium is quite regular in character, mitotic figures are very infrequent, and altogether there is nothing at all suggestive of malignancy.

(b) Endometrium.

The endometrial growth (figure 2) presents a totally different appearance. It is essentially papillary in structure with a fine con-

nective tissue stroma forming walls to its acini and a core to its papillary processes. The acini are lined and the papillary ingrowths covered by tall columnar epithelium several layers deep. The acini vary greatly in size and shape and the larger are filled with some sort of mucoid secretion. The epithelium, especially in certain parts of the growth, is very irregular, mitotic figures occur with great frequency, and the basement membrane is lost in places. The tumour, in fact, is clearly malignant, a papillary adenocarcinoma. For a malignant growth it is singularly well defined at its junction with the uterine muscle, but occasionally there is indubitable evidence of invasion. On its inner aspect, that is towards the cavity of the uterus, the growth is undergoing well-marked mucoid degeneration, and there is also a certain amount of necrosis with much polymorph infiltration.

(c) *Cervix.*

The cervical endometrium is slightly cystic and invades the muscle a little more deeply than usual, otherwise the cervix appears normal.

COMMENTARY ON THE CASE.

Besides the fact that two totally distinct neoplasms are here associated in the same uterus, the case is interesting on account of the unusual characters presented by the endometrial new-growth itself. A papillary adenocarcinoma like that shown in figure 2 is very rarely found arising primarily in the corporeal endometrium. A very similar condition is, however, figured and described by Cullen¹ in his monograph on cancer of the uterus, being regarded by him as of endocervical origin. In this case there is no evidence of such an origin, the cervical endometrium, except for some slight cystic change, appearing normal.

With regard to prognosis, it seems reasonable to assume that the greatly thickened adenomyomatous wall will constitute a more efficient barrier to the local extension of the malignant growth than would the ordinary myometrium, and in this case the patient is still free from any sign of recurrence ten months after operation.

REMARKS BY DR. STEWART ON THE FREQUENCY OF THE CONDITION.

In making an enquiry into the frequency with which adenomyoma of the uterus is complicated by the occurrence of malignant disease, one is met by the initial difficulty that reliable statistics are few and far between. In most cases the diagnosis of adenomyoma can only be made with certainty by a careful histological investigation of each myomatous uterus removed by the surgeon. In some instances the microscopic examination of a single portion of the tumour is insufficient for this purpose, inasmuch as the glandular

areas may be few in number, or even confined to certain parts only of the growth. As a rule, however, the microscopic diagnosis is easy, and one can only conclude from the enormous variation in the statistics of different observers that in the majority of cases no routine microscopic examination has been carried out. To this charge I must myself plead guilty. It has been my custom hitherto to examine microscopically only those cases of myoma uteri which exhibited some naked-eye peculiarity or variation from the "normal" appearance of such growths, and in this way a certain number of cases of adenomyoma may have been passed over undiagnosed.

For the purposes of this communication I have analysed all the specimens of myoma uteri investigated by my colleagues and myself in the Pathological Department of the General Infirmary at Leeds during the past three years. They number 100 in all, of which 52 have been examined microscopically. The results are as follows:—

Adenomyoma	4 per cent.
Carcinoma of Body	3 per cent.
Carcinoma of Cervix	2 per cent.
Sarcoma of Body	1 per cent.

Of the three cases of cancer of the body one was associated with adenomyoma, viz., that which has just been described, while the case of sarcoma was due to the secondary invasion of a myomatous uterus by a primary ovarian new-growth. Of the three remaining adenomyomata two were typical examples of the diffuse variety, while the third was an adenomyomatous polypus. These figures are of course too small to draw any conclusions from, but they are interesting for comparison with the collected figures of other authors, some of which may now be quoted.

Statistics the reliability of which appears to be beyond question are those of Cullen², who found that out of a total of 1,283 cases of myoma examined by him between April 1, 1893, and July 1, 1906, 73—that is, about 5·7 per cent.—were instances of adenomyoma. In this he included only interstitial, subperitoneal and submucous adenomyomata and large adenomyoma of the uterine horns. The small nodules so frequently found in the cornua were purposely omitted. Compare these with the collected figures of Tracy³ who found 19 cases of adenomyoma in 3,561 cases of "fibromyoma," or only ·53 per cent.

In Cullen's series, 10 out of the 76 cases of adenomyoma were associated with malignant disease of the uterus, viz., 6 with cancer of the cervix and 4 with cancer of the body. Of the latter, two were apparently independent neoplasms, while two arose, in part at least, from the glandular elements of the benign growth.

In a series of 16 cases of adenomyoma recorded by Grünbaum,⁴ one only was the seat of carcinomatous change.

With regard to the incidence of carcinoma in cases of uterine myomata generally, Tracy's collected cases, 3,561 in number, show 63 cases of cancer of the body and 25 of cervical cancer, while in a series of 4,880 cases of "fibroid tumour" collected by Noble,⁵ there were 75 cases of corporeal and 63 of cervical carcinoma. It is to be noted that the statistics of the two latter observers overlap; they are not dealing with totally different series. One may focus these figures by tabulating them as follows:—

	Carcinoma of body.	Carcinoma of cervix.	Total cases of carcinoma.
Cullen.	4 cases or	6 cases or	10 cases or
73 cases of adenomyoma...	5·5%	8·2%	13·7%
Tracy	63 cases or	25 cases or	88 cases or
3,561 cases of myoma ...	1·7%	·7%	2·4%
Noble.	75 cases or	63 cases or	138 cases or
4,880 cases of myoma ...	1·54%	1·29%	2·8%

While I feel strongly that the statistics collected by Tracy and by Noble are valueless as a guide to the frequency of adenomyoma, a condition which was only discovered within comparatively recent years, it is probable that they are quite reliable in so far as they deal with the incidence of malignant disease in cases of myoma, since this condition usually presents a striking and more or less characteristic appearance naked-eye. Cullen unfortunately does not analyse from this point of view the series of 1,283 cases of myoma from which his 76 cases of adenomyoma are taken, but nevertheless certain fairly definite conclusions may be arrived at from a comparative study of the above figures. Perhaps the most striking fact brought out by these statistics is that carcinoma occurs with much greater frequency in cases of adenomyoma than in cases of myoma. Carcinoma was five times more frequent in Cullen's series than in the collected series of Tracy and Noble, and the latter are of course inclusive of all adenomyomatous cases.

With regard to the situation of the malignant neoplasm, in the collected cases of myoma the body was the more frequently affected, in Cullen's series, the cervix. So far as the latter is concerned, one is perhaps hardly justified in drawing any definite conclusion from so few figures, especially as the difference is so small, but in the case of the earlier observation, on the absolute frequency of malignant disease in cases of adenomyoma, the difference is so striking as not to be explained away by any element of chance. The explanation is probably dependent on a variety of factors, but the two following may be suggested as of prime importance:—

(1) It has been shown by various observers in the case of other organs, *e.g.*, ovary, that carcinoma is not infrequently preceded by a benign epithelial overgrowth.

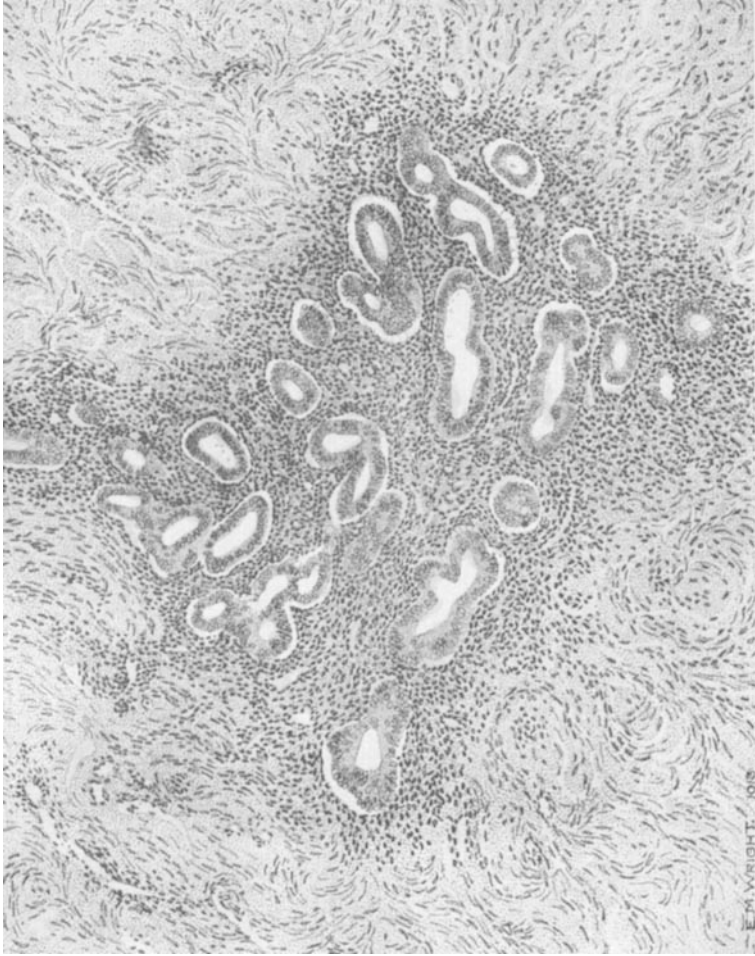


Fig. I.

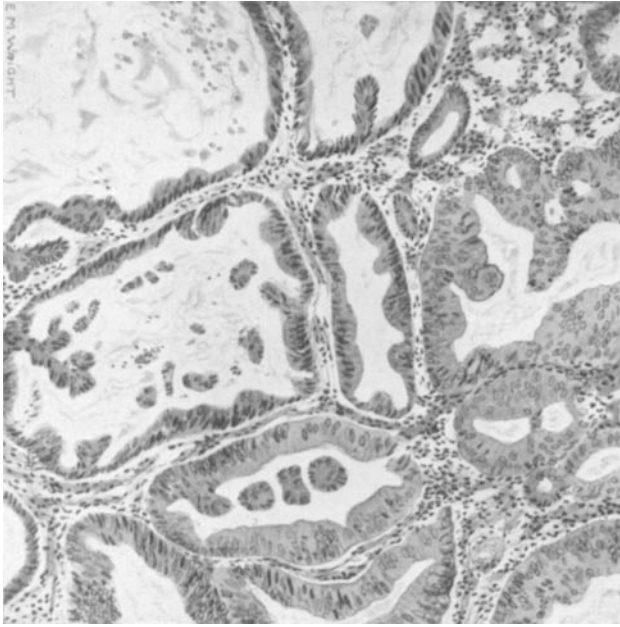


Fig. II.

Littlewood and Stewart: Adenocarcinoma of Uterus 401

(2) A study of the age incidence shows that adenomyoma tends to occur somewhat later in life than ordinary myoma, and consequently nearer the "cancer" age. This is shown in the following table:—

AGE INCIDENCE IN UTERINE TUMOURS.

	Myoma. 291 cases. (Noble)	Adenomyoma. 66 cases. (Cullen)	Carcinoma. 77 cases. (Sinclair). ⁶
Under 30	9	4	1
30 to 40	113	21	23
40 to 50	121	19	28
Above 50	48	22	25

In this connection it is to be noted that in the case which we have just detailed and in two out of the four similar cases described by Cullen, the malignant new-growth originated in the endometrium itself, and showed no evidence that it arose either in whole or in part from the epithelial elements of the adenomyoma.

REFERENCES.

1. Cullen. "Cancer of the Uterus," London, 1900, p. 587.
2. Cullen. "Adenomyoma of the Uterus," Philadelphia and London, 1908, p. 1.
3. Tracy. *Surgery, Gynecology and Obstetrics*, 1908, vol. vi, p. 246.
4. Grünbaum. *Münch. med. Woch.*, 1908, vol. xxi, p. 1156.
5. Noble. *Journ. of Obst. and Gyn.*, 1906, vol. x, p. 436.
6. Sinclair. "Malignant Growths of the Uterus," in "A System of Gynecology," edited by Allbutt, Playfair and Eden, second edition, 1909, London, p. 329.

DESCRIPTION OF PLATES.

PLATE 1. Section of the adenomyoma showing one of the adenomatous islets with endometrical-like stroma lying in the midst of the unstriped muscle of the uterus. The condition appears to be quite benign. (×60.)

PLATE 2. Portion of the endometrical new-growth, showing its adenocarcinomatous nature with mucoid degeneration. (×60.)