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Adenocarcinoma of the Endometrium

by

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A number of arguments about adenocarcinoma of the endometrium are still unresolved. However, in the past twentyfive years, the cure rates for the disease have very nearly doubled from about 40% to a present expectation of about 75%. Here, then, is a lesion in which it can be demonstrated that meticulous attention to detail has been rewarded most satisfactorily.

Etiology

This is a disease of relatively advanced age with a mean at about fifty odd years and a considerable scatter into the more advanced age groups. It presents, then, with the surgical problems of the handling of the degenerative diseases of advancing age. These include the usual cardio-vascular-renal lesions and obesity. One of the more intriguing is the abnormal frequency of diabetes. In our own material, this represents an incidence of about 10% with an additional group showing minor disturbances of carbohydrate metabolism. And the greater the obesity, the more likely is the association of frank diabetes. The Jewish woman shows an even greater incidence of the association. Kaiser found in a study of Jewish women with adenocarcinoma of the endometrium that practically all of them were either diabetic or had disturbed glucose tolerance curves. One cannot avoid the conclusion that there is a basic element of importance here which is not understood. The clinical significance, of course, lies in the indication for the routine search for one of these diseases in the known presence of the other.

The main argument has centered about the etiologic relation of endometrial hyperplasia and two of the rare causes of this in the Stein-Leventhal syndrome and the granulosa cell tumor of the ovary. A past history of endometrial hyperplasia can only be considered in the light of the fact that most women have endometrial hyperplasia at some time in their careers while adenocarcinoma of the endometrium is a relatively rare disease. The expectation, then, is that a considerable number of women with adenocarcinoma of the endometrium will give a history of previous endometrial hyperplasia just as will a considerable number of women with fractured leg bones. In order to test this, my colleague, Lowe, followed a group of some 120 women who had been treated at the University of Minnesota Hospitals for Menopausal hyperplasia from ten to twenty-five years previously. No adenocarcinoma of the endometrium had appeared in the group although only 85% of them could be traced.

A major cause of confusion lies in the problem of differential histologic diagnosis between these two lesions. Adenocarcinoma of the endometrium is a highly differentiated lesion which develops slowly and invades late. Endometrial hyperplasia often shows violent proliferation and since prolonged bleeding occurs, bacterial infection of the uterine cavity can add an epithelial cell polymorphism of sometimes striking degree. The benign lesion, then, may appear more active than the malignant. Experience has shown that diagnostic confusion is not unusual.

It is evident that endomehrial hyperplasia is not a so-called precancerous lesion and should not be treated as such. Where doubt arises in histologic differentiation, as it can, the injection of 25 or 50 milligrams of progesterone will produce a chemical curettage beginning five days later. The estrogen affected endometrium will be more or less cleanly shed. Curettage six weeks later will produce endometrium from which an objective diagnosis can be made.

Natural History

Adenocarcinoma of the endometrium begins as a highly differentiated intra-alveolar tumor. It may begin locally but is often seen in its earliest stages scattered widely over the endometrial cavity. Since it grows slowly and since it is protected from the outside world of infection and trauma, it breaks down late and slowly. The symptom of abnormal uterine bleeding is often minor at first and in the form of a "cherry water discharge". This has lead to the clinical rule that the smaller the amount of persistent postmenopausal bleeding, the greater the suspicion that adenocarcinoma of the endometrium is responsible and vice versa.

It can then grow to produce an exophytic mass which may fill or even distend the uterine cavity. It can spread on the surface to involve the whole cavity and may even grow as a superficial or cake-icing spread to the surface of the endocervix or portio. It usually invades the uterine masculature late. While this is far from being an absolute rule, it is usual and is one of the factors which allows good results from simple surgical procedures. When it does invade, it may extend through the uterine wall to give rise to a generalized abdominal carcinomatosis.

Metastatic spread is to the lymphatic glands of the whole area, the iliac and aortic glands are, of course, involved. There is a surprising frequency of obturator gland involvement and of metastases to the inguinal-femoral groups. An outstandingly important clinical feature is the frequency of vaginal metastases which, in our own material occurred before and after treatment in 12% of the patients. The frequency with which vaginal metastases or recurrences in the post operative vaginal stump proved to be associated with tumor involvement of the lower portion of the lower uterine segment or the endocervix justifies procedures for the determination of this involvement in each patient and separate handling of those with such involvement.

As the tumor develops, it loses its alveolar form and becomes more or less solid. This is an expression of age and thus of the likelihood of metastatic spread. It has, then, a prognostic significance. The more highly differentiated and alveolar the tumor, the more likely is it to be localized to the uterus and so the better the prognosis.

In the absence of gross spred from the endometrium, it is surprising how frequently fluid from the cul-de-sac taken at laparotomy, contains tumor cells on smear. About 40% of all adenocarcinomas of the endometrium will show this. It is clear that there is no necessary relation between such spill and the prognosis.

Diagnosis

Irregular bleeding from the uterus should be submitted to histologic diagnosis and there are very few exceptions to this rule. It applies with particular force to postmenopausal bleeding. And, as was pointed out above, the small bleeding is even more suspicious than profuse bleeding.

Unfortunately, smear diagnosis has proved to be only 85% reliable. A positive biopsy is diagnostic but a negative one does not exclude the disease.

A differential curettage should be done. This involves a separate specimen obtained from the endocervix since, as will be discussed under treatment, it is important to recognize endocervical involvement. It is also often impossible to differentiate histologically between adenocarcinoma of the endocervix and adenocarcinoma of the endometrium. The clinician, then, must be prepared to guarantee the site from which the specimen was obtained. The endometrium is then curetted. The cervix is biopsied as necessary. These are sent as three separate specimens. The vagina is very carefully searched for even the smallest lesions and these are biopsied if found.

It is often impossible to be certain of the significance of masses lateral to the uterus. These may be inflammatory or tumor spread. It is not unusual that laparotomy is justified to settle this point before giving up the problem as hopeless generalized abdominal carcinomatosis.

The remainder of the patient work up is that of the usual cancer problem.

Treatment

The arguments here have had to do with the value of post operative or preoperative irradiation of one sort or another, the type of surgical attack, the decision as to the use of routine vaginal irradiation and the handling of specific complications.

By observations on carefully controlled gamma irradiation dosage, it has become clear that about 12,000 gamma roentgens are required for about a 50% destructive rate in well established adenocarcinoma of the endometrium. This dosage can be supplied to the surface of the endo-

metrial cavity, the cervix and the vaginal lesions which are not more than about 3 cm. in diameter and 1 cm. deep. In the first two, this can be achieved with suitably distributed radium and in the vagina by surface radium or, in smaller lesions, by interstitial radium or radon. The maximum dose which can be ahieved by long focal distance therapy (X-ray or cobalt) is about 3,500 gamma roentgens over 28 days or, for comparison with radium as single dose therapy, something less than 2,500 gamma roentgens. This is a negligible dose and, while it can shrink most cancers, it is not curative for adenocarcinoma of the endometrium. The inverse square law protects the tumor at depth in the uterine muscle so that compound isodose curves show a grossly deficient dose even a very short distance beneath the endometrial-muscular junction and negligible doses at the peritoneal surface of the uterus. It is clear, then, that 50% survivals do not satisfy present cure expectations and that simple surgery can go more widely with tumor removal than can irradiation as limited by the anatomy of the site.

Various claims have been made for advantages from the addition to surgery of one form of irradiation or another. To this a study programme was set up. Older material had been treated by various irradiation techniques, which, it must be said, are unsatisfactory in the light of present knowledge. A 35% surgical rate had been applied. This is shown in line 1 and is used as a sort of control series. The first study group is shown in line 2. All patients in so far as possible, were treated with full dose x-ray, full dose radium from an adequate intrauterine distribution and about 8 weeks later, a 66% surgical rate was applied. Since X-ray was theoretically the least likely to be useful, the next series was arranged to withdraw routine X-ray, apply routine intrauterine radium to all patients and, by chance, a 67% surgical rate was applied. This is shown in line 3. The fourth series removed all routine irradiation except for special indications, and by now, a 94% surgical rate seemed justified. Line 4 shows this. The "5 year cure" rates for the various groups is shown in the last column. All patients have been followed.

Line	X'ray	Radium	Surgical rate	"5 year cure"
1-old (pre 1938)	+	+	35	42.5%
2	+	+	66	57%
3	0	+	67	56%
4	0	0	94	69%

The reader will recognize some desirable further investigations but two conclusions seem justified. There is no evidence that withdrawal of irradiation adversely affected the survival rates. The survival rates are directly related to the surgical rates. The surgery applied was simple panhysterectomy, bilateral salpingo-oophorectomy and the removal of a large vaginal cuff. The cuff was protected from implant metastases by packing the uterine cavity with tincture iodine soaked gauze, suturing the cervix and packing the vagina with a 2% neutral acriflavine emulsion soaked gauze.

Wertheim type dissections do not appear to be justified by the results but this should be proved in a comparable all-inclusive study. In these poor risk patients, this will either greatly reduce the surgical rate or grossly increase the procedural mortality rate. For the simpler procedure it has been proved possible to surgically treat more than 90% of the patients with a total mortality rate of 6% and a true surgical risk rate (removing those patients who died of tumor or after simple laparotomy to prove generalized abdominal carcinomatosis) of 2%.

Extension of tumor to the endocervix or portio accounts for the vast majority of cuff and adjacent upper vaginal metastases. For this reason, patients with such lesions are best irradiated pre-operatively with full dose x-ray and intra-

uterine, intracervical and intravaginal radium. There is evidence that this reduce the rate of such metastases although it increases the various risks associated with post operative radio-necrosis.

The vagina must be most closely observed at short intervals post operatively for the recognition of early metastases. These when small, may be treated with surface radium irradiation with a maximum focal distance and a carefully calculated depth dose of 12 — 13,000 gamma roentgens. The author applies all surface radium irradiation over 100 hours. Lateral wall metastases which are small and are not in continuity with bladder, urethra or rectum may be treated with similar dosages of interstitial radon from seeds of between 1 and 2 millicuries. Larger lesions may be shrunk to smaller size by long focal distance therapy and then treated with surface radium. All of these dosage calculations must be exact. Vaginal metastases are by no means hopeless particularly if the lesions be recognized while still small. The author has one patient who has had three separate crops of such metastases and is alive and clinically free of tumor five years after the treatment of the third crop.

For these reasons, routine post operative vaginal irradiation is not recommended. An adequate dose to the whole vagina produces automatic vaginal closure and makes detailed observation subsequently impossible.