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Early Detection of Cancer in the Female Genital Tract

by

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As cytology has been thrashed to some extent in the last few months, I would confine myself mainly to Morbid Anatomy. And as the subject matter is early detection of cancer, I will be speaking mainly on the differential diagnosis of early cancer, and I will pass only scantily over the established cancers.

Vulva: (1) The **inflammatory lesions,** Chancroid, Granuloma inguinale, Lymphogranuloma inguinale, Syphilitic chancre and Condyloma latum, are all sinister looking lesions in their advanced stage. However, a good history and histology will exclude these maladies from the realms of neoplasm.

(2) **Condyloma acuminatum.** This is a viral condition, which exacerbates with pregnancy and is in no way related to venereal disease. The lesion, under the microscope, shows a verrucous squamous papilloma, which grows above the skin surface like a shrub. It is benign and very rarely, if ever, shows a malignant change.

(3) **Lichen Sclerosus et atrophicus.** This name has replaced the other two conditions—atrophic leucoplakia and kraurosis, which are now shown to be variants of the same disease. This condition is seen usually around the vulva as coalescing plaques of thinned-out, greyish white, parchmentised areas in the post-menopause. Itching with fissuring may then ensue.

Histologically, a mild hyperkeratosis, marked atrophy of the epidermis an upper dermis showing oedematous collagenised change and a round cell infiltration of the lower dermis are seen. This picture is characteristic.

(4) **Leucoplakia.** This condition generally occurs in women who are past the menopause. The early red swollen areas give way to thick, raised white patches, which may spread down to the perineum. It usually eaves the vestibule and urethral orifice uninvolved.

The histology section shows (a) hyperkeratosis (b) acanthosis (proliferation of the prickle cells). (c) enlargement and elongation of the rete pegs, whose cells often show atypical changes with some mitotic figures and (d) a dense chronic infiltrate in the dermis. This lesion is precancerous and a malignant change supervenes on about 25% of them.

(5) **Bowen's Disease or Erythroplasia of Queyrat.** This is a carcinoma-in-situ or intraepidermal carcinoma of the vulva. A biopsy showing this picture does not exclude a frank invasive carcinoma in other parts of the vulva. Clinically one sees either a raised red patch, or a thickened, white, firm area, occuring in one or more areas. It is usually indistinguishable from leucoplakia. The diagnosis is a histological one.

The histological section shows hyperkeratosis, acanthosis and enlargement and coalescence of the rete pegs. The entire depth of the epidermis shows all the features of a carcinoma: loss of polarity up to the stratum corneum, dyskeratosis, and the numerous atypical cells with many mitotic figures give a "wind-blown" appearance.

The carcinoma may be confined by the basement membrane for years, but when it does invade, it usually ends up as a relatively poorly differentiated squamous cell carcinoma. However, as a pure carcinoma-in-situ, it is rather an uncommon lesion of the vulva.

(6) **Paget's Disease.** This is a rare disease secondary to underlying carcinoma of the ducts or

glands of exocrine or apocrine origin. The typical picture is that of individual invasion by the large, oval or round, pale cells (Paget's cells) in an otherwise normal epidermis.

(7) **Invasive Carcinoma.** This may be of two types:— (a) the much commoner squamous cell carcinoma, (b) the much rarer basal cell carcinoma. Any doubtful lesion must be biposied: a nodule, a raised plaque, a thickened white patch, an ulcer with rolled edges, etc. The histology of the above two lesions are too well known to merit a description here.

(8) **Vagina:** As primary carcinoma of the vagina is so rare and more than 90% of them is a squamous cell carcinoma, I would not dwell any longer in this region.

Cervix: (1) **Cervical polyp.** This is a very common condition and is often clinically diagnosable. It is often biopsied because sometimes a carcinoma of the cervix can be polypoid in form, and very rarely a malignant change may supervene on a benign polyp.

(2) **Pregnancy.** One of the changes in the cervix in pregnancy is a basal cell hyperplasia so that the squamous epithelium of the ectocervix can cover the exposed "adenomatous hyperplasia" of the endocervix which has everted. This basal cell hyperplasia may reach half way, but it may go right up the whole depth of the squamous epithelium. Together with the presence of few mitotic figures, a picture very similar to carcinoma-in-situ is depicted. However, it can usually be differentiated from the carcinoma by its monotony of the small dark-staining cells, whilst carcinoma-in-situ has much more atypism, pleomorphism and mitotic figures. Seeing that pregnant changes regress after delivery and carcinoma-in-situ runs a slow protracted course, a wait-and-see attitude is advisable in case of doubt. A cone biopsy can be safely used to exclude invasive carcinoma even during pregnancy. If no invasion is present, then re-assessment of the case can be made after delivery.

(3) **Squamous Metaplasia.** This is a replacement of the normal columnar epithelium of the endocervix and its glands by squamous epithelium. This occurs most frequently near the squamo-columnar junction during pregnancy and after erosions. It takes place by (1) regeneration of the reserve cell (basal cell) of the endocervix or (2) squamous emigration from the ectocervix. The basal cell hyperplasia may dip into the stroma as clusters of grapes, simulating the basal cell carcinoma of skin. These small clumps of uniform basal cells near the regions of chronic cervicitis must not be interpreted as early carcinoma. Squamous differentiation takes place later from these basal clumps. Further, when crypts and glands show metaplasia only in parts of their perimeters, a picture, to the uninitiated, may suggest early carcinomatous invasion. As squamous metaplasia, like chronic cervicitis, is so common (quoted as 70% to 80% of all cervical specimens biopsied), one must recognise that it is completely benign in nature.

(4) **Atypical epithelial hyperplasia.** This condition cannot be recognised with the naked eye. It is purely a histologist's diagnosis. It occurs again around the squamo-columnar junction and is usually associated with inflammation and pregnancy. The changes are more aggressive than the above two conditions just described. Besides the basal cell hyperplasia, many of the cells show plemorphism with large hyperchromatic nuclei and some mitotic figures. A hard and fast rule cannot be ennunciated here as regards its distinction with carcinoma-in-situ. However, the general distinguishing factor is how far up these changes take place. It it involves the entire thickness of the surface epithelium, then one may call it carcinoma-in-situ, and anything up to that point, one may subdivide them into mild, moderate and severe atypical hyperplasia. So from this description it would appear that severe atypical hyperplasia merges imperceptibly into carcinoma-in-situ. This is now generally accepted by most pathologists, but each pathologist has its own line of demarcation to differentiate the benign from the malignant. As there is always a greater tendency to overdiagnose malignancy, the clinician is urged to send a cone biopsy for confirmation in all cases of carcinoma-in-situ and severe atypical hyperplasia.

(5) **Carcinoma-in-situ** (Intra-epithelial carcinoma). Clinically the cervix looks normal or eroded. It is diagnosed only by the microscopist. The commonest site is at the squamo-columnar junction.

Histologically, it should have all the characteristics of malignancy except that it is limited by the basement membrane of the surface epithelium. Usually there is loss of polarity of the whole depth of the epithelium. The cells and nuclei may either

have their long axes perpendicular to the surface line, or there is total disarray with no order of the cells. Pleomorphism, giant and bizarre cells and numerous mitotic figures are the other features. The nuclei usually occupy more than half the cell and pink, distinct nucleoli are plentiful. A thin superficial layer of mature squamous cells of one or two cell thick may not disqualify the diagnosis of intra-epithelial carcinoma, especially when they do not appear to be differentiated from the malignant cells below, i.e. they appear to belong to the pre-existing population of benign epithelium, because of the abrupt change.

Sometimes an associated brisk chronic inflammatory process may tend to dissociate a rete peg, and thus a diagnosis of early invasion could be erroneously pronounced.

(6) **Carcinoma of the cervix.** Grossly a growth can usually be seen, as 80% occurs at the ectocervix and 20% occurs at the endocervix (Way 1951). The cervix may be badly ulcerating or a fungating growth may be seen, or a barrel-shaped enlargement of the cervix with a mucoid appearance, is the other picture.

Histologically 95% of the carcinomas of the squamous type and 5% is of the adenocarcinomatous type. The squamous cell carcinoma is usually moderately to poorly differentiated.

Endometrium

(1) **Polyps and endometrial hyperplasia.** Polypoid endometrium is usually the result of endometrial hyperplasia, and the histology of both are usually identical. However, there is also a proportion of polyps that show cyclical changes, and others show dormant glands in the post-menopausal.

The cause of endometrial hyperplasia is usually due to prolonged oestrogenic stimulation. This may be due either to (1) follicular cysts (2) feminizing tumours of the ovary and (3) extra-ovarian (? adrenal). It occurs at any age after puberty: there is a concentration at the perimenopause and a smaller one soon after puberty. Post-menopausal cases are not infrequently seen.

There is an increase in thickness of the endometrium. The glandular picture is due to a prolonged follicular phase, when the cells are larger, the glands show cystic dilatation, and mitotic figures and reduplication of epithelium are the hallmarks in histology. These changes are patchy and so is the stromal hyperplasia. Therefore varying sizes and shape of glands give the "Swiss-cheese" pattern. Blood vessels are scanty, and no luteal secretion is seen. Cilia formation is a very frequent finding.

(2) **Atypical Endometrial Hyperplasia.** Very few cases have been diagnosed, because they have invariably been diagnosed as adenocarcinoma. Indeed, the borderline between this condition and malignancy is so thin, that one wonders whether it exists. On the other hand, those cases where the curettage alone was diagnosed as a doubtful adenocarcinoma, and the hysterectomy specimen bears no trace of any malignancy, may truly belong to this category.

The histology here is a back-to-back crowding of dark-staining glands of irregular sizes and shapes. They may be lined by many layers of cells with many mitotic figures. The cells are even larger than the simple hyperplasia.

The course of treatment may be made much easier if the woman is perimenopausal, but it is most difficult if she is in the early thirties and wants more children. A discussion between the gynaecologist and the pathologist is most warranted here.

(3) **Carcinoma.** Although usually the uterus may be found to be enlarged by the endometrial carcinoma, sometimes it is normal, or even smaller. It is a much rarer neoplasm than carcinoma of the cervix and has a better prognosis than the latter.

The histology is an obvious adenocarcinoma and sometimes papillary in structure. Only a very small percentage of cases belong to a pure squamous cell carcinoma. There are also areas of squamous metaplasia found in the adenocarcinoma: these areas when plentiful, the name of adeno-acanthoma is applied. This carries a better prognosis. However, when an adenocarcinoma and a squamous carcinoma co-exist (which may be due to cancerization of the cervix and endometrium) the prognosis is no better and may be worse.

Ovary

Carcinomatous change in mucinous (pseudomucinous) and serous-cystadenoma.

These two cystic tumours are the commonest ovarian tumours, and they occur about the same frequency.

(1) The **mucinous cystadenoma** is a large multiloculated tumour usually occuring unilaterally. It classically contains mucinous fluid. Histologically, it is lined by a tall columnar cell whose nucleus is pressed to the base, and the cytoplasm is clear and glassy. An early malignant transformation can only be diagnosed with certainty when small areas show the following changes: the cells now become cuboidal, the glassy cytoplasm gives way to a more eosinophilic and granular one, there may be more than one cell thick, and mitotic figures begin to appear. In the overtly malignant cases, all the characteristics of malignancy appears and it may be difficult to differentiate it from a de novo adenocarcinoma. This change, however, is much less frequent (5-12%) than in the serous cystadenoma.

(2) The **serous cystadenoma** is usually unilocular or bilocular and occurs bilaterally in half the cases. They are small or of moderate size, and papillary projections into the cystic cavities are a frequent feature. The fluid is thin, serous and clear. Histologically, the cellular lining is either cuboidal or of the tubal variety. The papillae are also covered by the same epithelium and their cores are fibrous. The malignant change into a *serous cystadenocarcinoma* is usually a histological subtlety. It is the commonest malignant tumour (60% of ovarian carcinomas) in the ovary. Grossly when multitudes of projections are seen on the surface, a malignant suspicion may be cast. The frankly malignant ones are of no problems under the microscope. The boderline ones tend to show multilayering of cells, larger cells with more prominent nucleoli, hyperchromatism and very early invasion of the stroma. The increase of mitoses and number of papillary projections may help one to decide on its malignant nature.

N.B. The above talk was richly illustrated with lantern slides, but I apologise that owing to the pressure of work, no pictures are produced in this bulletin.