Morular metaplasia of the endometrium misdiagnosed as adeno-acanthoma in a patient with tubal pregnancy

A case report

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Summary

A 41-year-old woman underwent a fractional dilatation and curettage for menorrhagia and a diagnosis of adeno-acanthoma was made from the curettings. However, the subsequent hysterectomy and bilateral salpingo-oophorectomy specimen revealed the presence of a clinically undiagnosed tubal pregnancy and extensive immature squamous metaplasia (morules) of the endometrium. No malignancy was present. A review of the original curettings lead to the recognition of the benign lesion already present at that stage. Difficulties in the differential diagnosis are discussed. The presence of endometrial polyps is considered as a possible factor responsible for the morular metaplasia rather than the tubal pregnancy, which seems to be a previously undescribed and interesting coincidence.

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Immature squamous metaplasia (morular metaplasia) of the endometrium has been described in a variety of conditions including adenomatous hyperplasia,[1-4] endometrial polyps,[1] intra-uterine devices,[5] polycystic ovarian disease,[6] adenocarcinoma,[4,7] vitamin A deficiency[8] and even in normal endometrium.[1] It is very often misdiagnosed as malignant tumour tissue,[2,3,6] as in the case reported here. Recently morules have also been described in benign and malignant neoplasms of the colon.[9]

A case of extensive morular metaplasia of the endometrium, which was found in retrospect in the hysterectomy specimen, and the unusual occurrence of a coincidental undiagnosed tubal pregnancy found at operation are described. The possible pathogenesis of the morular metaplasia is discussed.

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Case report

A 41-year-old woman was seen at the gynaecological clinic of Tygerberg Hospital with progressively worsening menorrhagia over the previous few months but no previous amenorrhoea. Her last menstrual period had occurred 1 week before admission and had contained blood clots.

The rest of the medical and gynaecological history was not relevant, and she had no recent history of taking medication. She had an enlarged and irregular uterus (± 12 weeks' gestation in size), firm and not fixed. Vulvar, vaginal, rectovaginal and adnexal examinations yielded negative results. Laboratory investigation showed haemoglobin 9 g/dl and signs of iron deficiency anaemia.

She received 2 units of blood, oral ferrous sulphate and vitamin C. She was then re-examined under anaesthesia; hysteroscopy and fractional dilatation and curettage were performed. The uterus felt irregular, the cavity measured 13 cm and showed a polypoid, whitish area in the endometrium posterolaterally. The lesions were interpreted as leiomyomas and endometrial carcinoma. Bulky curettings were removed from the uterus. Histopathological examination of the specimen showed a proliferative endometrium with large areas of disturbed architecture owing to a florid glandular neoplastic process with marked squamous metaplasia (Fig. 1). The results of the examination were interpreted as showing a well-differentiated adenocarcinoma with squamous metaplasia (adeno-acanthoma). An endometrial polyp was also present.

Fig. 1. Curettings diagnosed as adeno-acanthoma showing the intricate glandular architecture. Squamous metaplasia (top arrow). **Note tubal metaplasia in gland** (lower arrow).

Five weeks later a hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus showed several leiomyomas, the largest measuring 7 cm in diameter. The endometrium was thickened and irregular, mainly in the upper area, the right tube had a swelling of 1,5 cm in diameter in the isthmic region and a corpus luteum was present in the left ovary. Histologically, the endometrium was in late secretory phase with areas of hypersecretion and decidual change. In addition there were areas of immature squamous metaplasia (morules) present in and around glands that

had a more pseudostratified epithelium and did not show secretory changes as did the adjacent glands (Figs 2 and 3). Several benign leiomyomas were present, as well as adenomyosis. The right tube contained an unruptured pregnancy (Fig. 4); the left ovary contained a corpus luteum. The other adnexal structures were normal. No adenocarcinoma could be found. In view of these findings the slides of the previous scrapings were re-evaluated and it then became apparent that the disturbed architecture, squamous metaplasia and glandular proliferation had been incorrectly diagnosed and that the process was in fact one of extensive morular metaplasia and not an adeno-acanthoma.

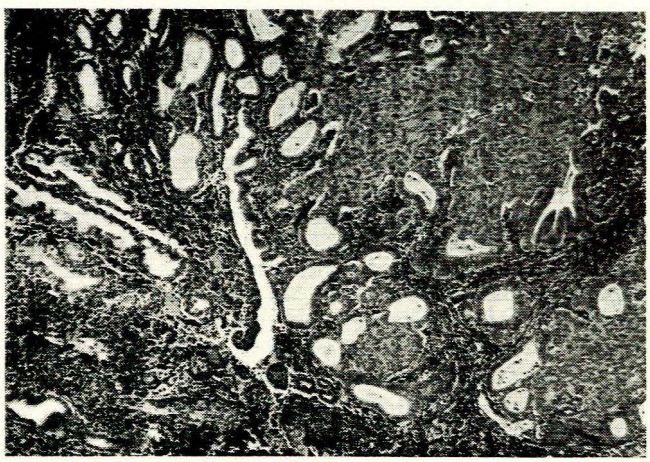

Fig. 2. Hysterectomy specimen with extensive morular metaplasia. Note the hypersecretory glands (centre left).

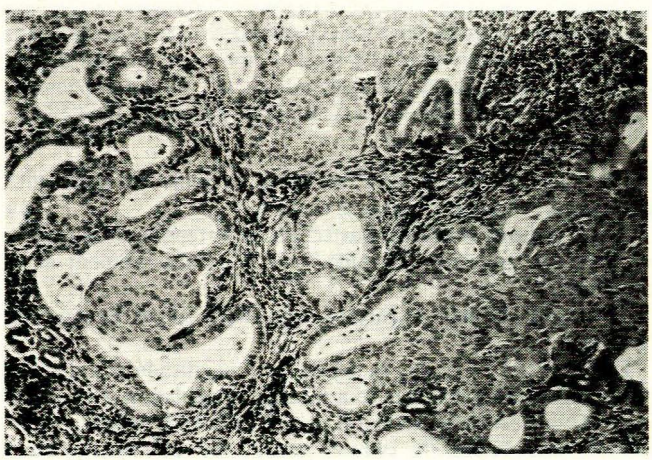

Fig. 3. Hysterectomy specimen showing the interglandular morules and benign-looking glands with early tubal metaplasia in places.

The patient made an uneventful recovery and 1 year after the operation was still free of disease.

Discussion

The Müllerian epithelium of the genital tract not only has the capability of local interchange but also of metaplasia. The most important metaplastic processes are clear cell and squamous cell metaplasia.[10] In the endometrium squamous metaplasia occurs occasionally in a variety of conditions and is divided into two types — mature and immature.[11] The mature type consists of keratinizing squamous epithelium. The immature type, called morules by Dutra,[3] consists of groups of plump to spindly cells without keratinization or prickle formation, and often gives rise to incorrect diagnosis as adeno-acanthoma.[2,6] There are several reasons for this:

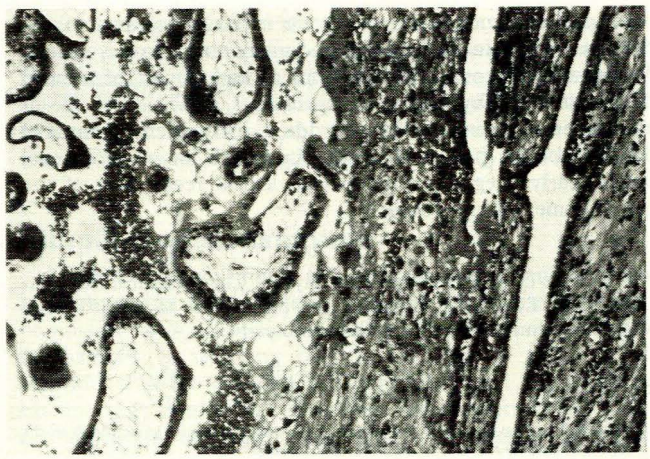

Fig. 4. Right tube with chorionic villi on the left and the wall of the fallopian tube to the right.

Disturbed architectural glandular pattern resulting from metaplastic change. When morules form, they either grow into the lumen of a gland or they extend from gland to gland. Both growth patterns lead to compression of the glandular lumina, forming budding-type pictures and a back-to-back appearance. This can be misleading and a well-differentiated adeno-acanthoma may be simulated.

Coincidence of other lesions posing a diagnostic difficulty *per se*. Although the actual aetiology of morular metaplasia is unknown, it seems to be due to some hormonal influence. Both oestrogen and progesterone have been found to cause the change not only in animal experiments,[12–15] but also in humans.[6] Excess oestrogen also causes adenomatous hyperplasia, often seen together with morules and sometimes referred to as adeno-acanthosis.[2] The histology of adenomatous hyperplasia often poses a diagnostic difficulty — even more so when compounded by morules.

Common occurrence of squamous metaplasia in true malignant lesions. Adenocarcinomas of the endometrium have a uniform appearance; 50% of well-differentiated adenocarcinomas contain foci of squamous metaplasia.[4] This common phenomenon together with the rather unusual occurrence of morules in benign lesions may lead to a prejudiced approach to diagnosis. There should, however, be no serious difficulty in recognizing the benign nature of morular metaplasia, as has been stressed repeatedly.[2,4,6] With careful examination of the surrounding glands, it will be obvious that however intricate and distorted the architecture may be, the cytological appearance of the epithelium is benign with no hyperchromasia, pleomorphism or abnormal mitotic activity. However, tubal metaplasia[6] or pseudostratified endometrial epithelium[2] is often seen.

There was another interesting aspect to the possible aetiology of the lesion in our patient. Was the morular metaplasia caused by the early ectopic pregnancy or the presence of endometrial polyps? The case reported by Bomze and Friedman[1] of a patient with morular metaplasia and a placental polyp seems to be the only published example of a combination of morular metaplasia with pregnancy, and these authors consider it coincidental rather than causative. In our patient the tubal pregnancy seems unlikely to have been the cause of the changes, at least in the curettings. The endometrium at that stage was in a proliferative phase and the patient probably conceived shortly after the first surgical intervention. The other possible reason for the metaplasia is more plausible, namely the endometrial polyp present in the scrapings. In fact,

the squamous metaplasia was seen in large portions of the polyp as well as in the adjacent endometrium. Morules usually disappear with conservative treatment and cannot be seen in the subsequent hysterectomy specimens.[1,3] The presence of morules in our patient might be due to incomplete removal of the stalk of the polyp during the curettage, or her hormonal status (early pregnancy) may have led to recurrence of the previous metaplastic process.

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Epidemiological research methods

Part II. Descriptive studies

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Descriptive studies are used to quantify the extent of a health problem in a population.[1] Their use, and the types of research questions that can be answered by them, are illustrated by two local studies.

In the first, 'A comparison of the mortality rates of various population groups in the RSA', health problems of the national population were of interest:[2] 'Before health priorities can be determined and the health resources deployed to the best advantage, it is necessary to know what the major disease problems are. This should be based on a knowledge of the pattern of mortality and morbidity in the population.'

In the second study, 'Hypertension management and patient compliance at a Soweto polyclinic', problems in health care delivery to a specific patient population were of interest:[3] 'Before starting to look for undiagnosed hypertensives in the community we decided to determine whether the service was dealing satisfactorily with its current hypertensive patients.... We therefore designed a study to answer the following specific questions...:

1. Do the Senaoane polyclinic staff measure the blood pressures of adult patients attending for the first time?
2. Do primary health care nurses manage these "first-visit" patients in accordance with the blood pressure management protocol they have been trained to use?
3. Do patients who have started antihypertensive drug treatment return regularly for blood pressure measurement and treatment?
4. If they return regularly, are their blood pressures lowered?'

In a descriptive study, therefore, the magnitude and distribution of a health problem in a specified population is studied in terms of TIME (when did it occur?), PLACE (where did it occur?) and PERSON (which groups are affected?). The design starts with an idea that occurs to the researcher about a particular problem. This is followed by selecting a group of individuals to be studied (sampling), considering which attributes to measure (measurement), describing the findings, and finally drawing conclusions on the basis of the findings. Commonly, new ideas or hypotheses are generated in this final stage, usually regarding possible explanations for the health problems described (cause-effect relationships). Such relationships may be attempts to explain the aetiology of diseases or the effect of preventive, curative or rehabilitative measures.

Important issues affecting the reliability of the sampling and measurement processes are discussed, some descriptive statistical measures demonstrated and how conclusions are affected by these, are indicated.

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Sampling

It is usually not practical or financially feasible to carry out measurements on the entire population. Therefore epidemiologists usually make their measurements on a sample or subset