Endometrial metaplasia

Helen F Stringfellow

Victoria J Elliot

Abstract

Epithelial metaplasia refers to the replacement of normal epithelium at a given site by mature benign epithelium inappropriate to that site. The endometrium is not unique in that it too demonstrates a spectrum of metaplastic epithelia. Some of these cytoplasmic alterations are better termed "changes" as they are thought not to represent true metaplastic transformation of the endometrial epithelium. The terminology is rather confusing as these two terms have been used interchangeably in the literature. This process may be encountered in benign conditions but can also be seen in association with endometrial hyperplasia and adenocarcinoma. The presence of endometrial metaplasia can significantly complicate the histological interpretation of endometrial biopsy material due to glandular architectural complexity and crowding which can lead to an erroneous diagnosis of endometrial hyperplasia or even carcinoma if the pathologist is unaware of the potential pitfalls. Endometrial metaplasia although commonly seen involving endometrial epithelium, may also on occasions involve the stroma. This review will describe the spectrum of histological features that can be seen in endometrial metaplasia of both epithelium and stroma and will aim to emphasize those histopathological features that will be helpful in distinguishing endometrial metaplasia from hyperplasia and carcinoma.

Keywords endometrium; eosinophilic syncytial change; metaplastic phenomena; squamous morules; stromal metaplasia

Introduction

Metaplasia is defined as "transformation of cells to a type not normally found in an organ". Tissues derived from the Mullerian duct system have the potential to differentiate along any of the forms of tissue found in the Mullerian system and also, rarely, to tissues found in the gastrointestinal tract and lower urinary tract. Therefore all forms of endometrial metaplasias would be best described as aberrant forms of differentiation in preference to metaplasias. The term "epithelial cytoplasmic change" is preferable. Throughout the pathological literature the term endometrial metaplasia has become well established. For the purposes of consistency, the use of this term has been retained in this review, despite misgivings of its terminological accuracy.[1,2]

The phenomenon of endometrial metaplasia was first described comprehensively by Hendrickson and Kempson in 1980.[3] Metaplasia in the endometrium can occur in both the epithelium and rarely the stroma.

The pathologist must be aware of the spectrum of endometrial metaplasias encountered and the clinical setting in which they may occur. They may be associated with a wide range of endometrial pathology, from benign to malignant conditions. These endometrial biopsies are often the most diagnostically challenging to the pathologist and their interpretation is further complicated by the co-existence of endometrial hyperplasia which is not an infrequent finding. Metaplastic conditions can sometimes impart a most alarming histological appearance to the endometrial biopsy, in particular when the changes have been exaggerated through the use of exogenous hormones. This may lead to an erroneous diagnosis of endometrial hyperplasia, or even carcinoma,[4,5] with an unnecessary consequential hysterectomy.

The aetiology of metaplasias, hyperplasias and carcinomas is similar in that unopposed oestrogen stimulation, tamoxifen and the use of HRT are common to both processes. Endometrial metaplasias therefore often coexist with hyperplasias and carcinoma.[6–9] Cases of endometrial complex atypical hyperplasias and well-differentiated adenocarcinomas treated with progestogens demonstrate metaplasia in 89% and 92% of cases in followup biopsies.[10]

Endometrial metaplasia may also seen in association with chronic endometritis, intrauterine devices, endometrial polyps, endometriosis and can be idiopathic.[11] In a recent study 55% of endometrial samples from patients who had Mirena intrauterine devices inserted exhibited metaplastic changes. The Mirena intrauterine device had been in-situ for 12 months in the majority of patients in this series.[12] Metaplasias have also been associated with selective progesterone receptor modulators.[13]

All endometrial biopsies containing areas of metaplasia must therefore be interpreted with great caution and in the context of appropriate clinical and demographic information to exclude more ominous pathology.

Endometrial metaplasia falls into two categories: epithelial metaplasias and those affecting the endometrial stroma. Epithelial metaplasias are the most common and will be discussed first. The pathologist must also be aware of the types of stromal metaplasia and these will be briefly discussed at the end.

Origins of metaplasia

It is thought that the cell of origin is a basal cell or reserve cell, similar to that seen in the cervix. These cells can be recognised by p63 immunohistochemistry and are conspicuous in the fetal uterus.[14] These cells remain in the cervix where they are easily identifiable but are not recognisable in the endometrium in adult life. Immunohistochemistry with p63 does demonstrate scattered positive cells in proliferative glands and p63 positive 'reserve' cells can also be demonstrated in postmenopausal endometrium. It has therefore been suggested that the columnar epithelial cells of the endometrium, under certain conditions of hormonal alteration, can form reserve cells. It is also hypothesised that metaplasias may also occur directly from the endometrioid cell without the formation of reserve cells.[15]

Squamous metaplasia

Squamous metaplasia is probably the most common of the endometrial metaplasias encountered. It is seen frequently in

Helen F Stringfellow *BSc (Hons) FRCPath is a Consultant Gynaecological Pathologist at Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Preston, Lancashire, UK. Conflicts of interest: none.*

Victoria J Elliot *BSc (Hons) FRCPath is a Consultant Gynaecological Pathologist at Southampton University Hospitals NHS Foundation Trust, Southampton, UK. Conflicts of interest: none.*

endometrium subject to unopposed oestrogenic stimulation and can be seen in association with progestogen therapy.[16] It can also be found in association with a wide range of histological changes, ranging from benign reactive conditions, for example associated with intrauterine devices, chronic endometritis and trauma, usually seen post curettage, to neoplastic processes.

It is of two main types. The first is typical squamous differentiation with squamous features in the form of keratinisation, intercellular bridge formation and/or prominent cell membranes. This may be seen lining the surface endometrium of the uterine cavity, sometimes involving the superficial endometrial glands. It comprises stratified squamous epithelium in which keratinisation is a conspicuous feature. This distribution of squamous metaplasia is almost exclusively seen in the elderly and is not infrequently associated with chronic irritative conditions such as prolonged preceding chronic endometritis or pyometra. This entity is known as ichthyosis uteri.[17,18] Amigo et al. have described a case of diffuse endometrial squamous metaplasia after resectoscopic myomectomy following treatment with a GnRH agonist.[19] Diffuse endometrial squamous metaplasia should also be differentiated from secondary involvement by cervical squamous neoplasia.

The second is squamous morule formation, so called because of their three-dimensional resemblance to mulberries. These morules have a characteristic morphological appearance, forming sheets of eosinophilic cells, with indistinct cell margins and rounded, ovoid or spindled nuclei (Figure 1). The cells are cytologically bland with no mitotic activity.[1,2] More importantly, the features of obvious squamous differentiation, such as keratin formation, intercellular bridges or the presence of prominent cell membranes, are not seen. It has therefore been previously suggested that they exhibit incomplete or immature squamous differentiation.[20]

Morular squamous differentiation is seen in about a quarter of endometrioid adenocarcinomas, in cases of benign nonhyperplastic endometrium, as well as in cases demonstrating architectural atypia ranging from simple and complex hyperplasia to complex atypical hyperplasia.[21] On rare occasions, the morules may entirely replace the glandular elements obscuring the underlying glandular pathology. Central necrosis (Figure 2) may be evident within these morules. Thorough sampling of the hysterectomy specimen in these situations usually reveals some glands that have not been replaced and allows adequate morphological assessment.

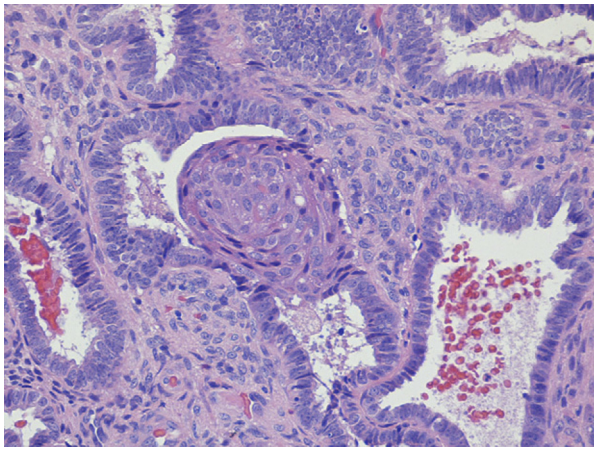

Figure 1 Isolated morular metaplasia filling the glandular lumen.

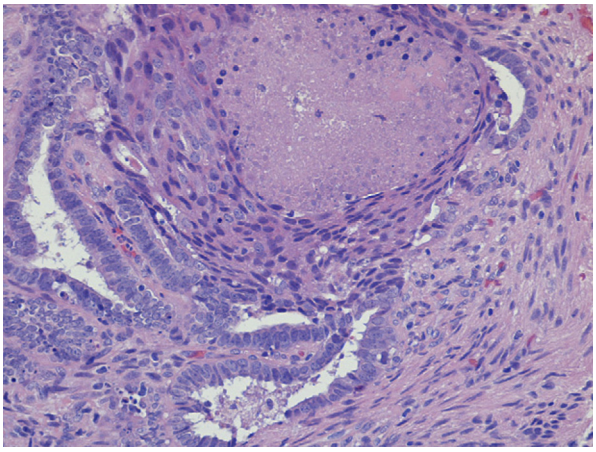

Figure 2 Morular metaplasia with central necrosis, a common finding.

Recently, Houghton et al. undertook a detailed immunohistochemical study comparing typical squamous elements with morules.[22] They used a panel of immunohistochemical markers incorporating b-catenin, oestrogen receptor (ER), CD10 and CDX2 an intestinal transcription factor, p63 and high −molecular weight cytokeratin LP34 were also used. The latter two markers are characteristically positive in mature or immature squamous epithelium respectively. Their study demonstrated that the morules typically exhibited diffuse nuclear CDX2 and b-catenin immunoreactivity and were positive for CD10 and LP34. They were usually negative for ER and p 63. In contrast, the morphologically typical squamous elements were usually ER, CD10, p63 and LP 34 positive. They were usually CDX2 negative or focally positive and exhibited no nuclear immunoreactivity for b-catenin. Furthermore, electron microscopy demonstrated that the morules possessed epithelial features but no ultrastructural evidence of overt squamous differentiation was demonstrated. However, in this study, immature squamous differentiation could not be excluded. In their opinion, given that there is no definite evidence of squamous differentiation within the morules by morphology, immunohistochemistry or ultrastructural examination (notwithstanding the possibility that the morules may represent foci of very early squamous differentiation) they suggest that the term "morular metaplasia" be used in conjunction with the associated glandular lesion e.g. endometrioid adenocarcinoma with morular metaplasia, until further studies establish the true nature of the morules.

Lin et al. have reported a study in which they tested the hypothesis that morules predict cancer risk.[21] They concluded that the glandular components had abundant oestrogen and progesterone receptors and high levels of mitotic activity, whereas the squamous morules were devoid of sex hormone receptors and had undetectable or extremely low proliferation rates. When mutated, the same PTEN mutation was detected in squamous and glandular elements, indicating that they are of common lineage. The cancer risk is associated with the atypical features exhibited by the glandular elements. It is the glandular elements that retain the competence to respond to the cancer promoting effects of oestrogens or the involuting effects of progestagens.