Pseudoneoplastic lesions of the uterine cervix

Kruti P Maniar

Peter Schlosshauer

Abstract

The differential diagnosis of malignant and premalignant lesions of the uterine cervix includes numerous non-neoplastic conditions which may show overlapping morphological features. Recognizing these mimics is crucial in order to spare the patient unnecessary surgical procedures with potential side effects, as well as the psychosocial consequences associated with the diagnosis of HPV-infection and/or (pre)malignancy. This article reviews benign entities that may be mistaken for neoplastic lesions of the cervix. Conditions of the ectocervical squamous epithelium, the endocervical glandular epithelium and the cervical stroma are systematically discussed in the context of the respective (pre)malignant lesion that they may be confused with, including low and high-grade squamous intraepithelial lesions, invasive squamous cell carcinoma, adenocarcinoma in-situ, various types of invasive adenocarcinomas, and sarcomas. Emphasis is placed on those features that help distinguish pseudoneoplastic lesions from true neoplasms, including clinical information, morphologic findings and ancillary studies.

Keywords adenocarcinoma in-situ; atypia; cervix; metaplasia; hyperplasia; pseudoneoplastic; squamous cell carcinoma; squamous intraepithelial lesion; invasive adenocarcinoma

It is very important to correctly identify malignant and premalignant lesions of the uterine cervix. But it is equally important not to overtreat benign lesions that may mimic true neoplasms. Even "minor" surgical interventions like LEEP or cone procedures are associated with potential side effects, especially cervical insufficiency during subsequent pregnancies, and should be avoided if possible.[1] Also, the diagnosis of an HPV-associated lesion immediately places the patient into an "STD" category, which may have far reaching psychological, interpersonal and/or marital consequences.

Ectocervical/squamous lesions

Mimics of low-grade squamous dysplasia (LGD)

Prominently **glycogenated or vacuolated squamous cells** may be mistaken for koilocytes. While both share a perinuclear cytoplasmic clearing, LGD associated koilocytes also display nuclear atypia (nuclear enlargement, angulation, hyperchromasia) and convey a certain architectural disarray of the epithelium. In contrast to benign epithelium, koilocytosis is often focal and demarcated from normal epithelium.

Areas of **hyper- and parakeratosis** are frequently biopsied due to an abnormal appearance on colposcopy. Both are nonspecific per se, but can give rise to abnormal cytology results and may be associated with dysplasia.

Bi- and multinucleation is a frequent finding in LGD. However, occasional binucleated cells are present in normal squamous epithelium and are nonspecific, unless they exhibit koilocytic nuclear atypia. Multinucleation is also seen in non-HPV associated viral infections, especially herpes simplex. Herpetic ulcers are severely inflamed; their multinucleated epithelial cells demonstrate nuclear moulding, chromatin margination and "ground glass" appearance.

Mimics of high-grade squamous dysplasia (HGD)

In post-menopausal patients, **atrophy** of the cervical squamous epithelium should always be considered in the differential diagnosis of HGD. Due to decreased oestrogen levels, atrophic epithelium is composed of immature appearing basal and parabasal cells lacking glycogen. Absence of cytologic atypia, rare if any mitoses without atypical forms, and preservation of cellular polarity favour a benign diagnosis.

Immature squamous metaplasia is frequently seen in cervical biopsies, partly because it is highlighted by acetic acid during colposcopy. Unlike its mature counterpart, it lacks glycogen, has a higher nuclear-to-cytoplasmic ratio, and may demonstrate a failure of the cells to align horizontally, leading to diagnostic confusion with HGD. Occasional mitoses may be seen, but the absence of atypical mitoses or the degree of atypia seen in HGD help to differentiate these lesions.

The term "**atypical immature metaplasia**" (AIM) is used for lesions that display some but not all features of HGD. It is not clearly defined and likely comprises a heterogeneous group of lesions, ranging from reactive atypia to true HGD. Due to the lack of consensus on the features and clinical significance of AIM, it is prudent to avoid this term as a diagnosis and rather attempt to reclassify the lesion. Helpful ancillary studies include HPV typing and immunostains for p16, Ki-67 (detected by the Mib-1 antibody) and ProEx C, which, if positive, favour a diagnosis of HGD. Negativity for these markers indicates a benign/reactive process. Cases negative for p16 but showing an increased Ki-67/ProEx C proliferative index may represent epithelial regeneration, while lesions positive for p16 but negative for Ki-67 have been interpreted as potential precursors of HGD or regressing HGD.[2–5]

Transitional cell metaplasia (TCM) can be seen in biopsies from peri- and post-menopausal women, often in association with atrophy, and may cause abnormal cytology findings. TCM resembles hyperplastic urothelium and may involve both ecto- and endocervix, with extension into glands. The characteristic lack of maturation can cause diagnostic confusion with HGD. Features favouring TCM include a lack of significant cytologic atypia or mitotic activity, the presence of longitudinal nuclear grooves, a "streaming" appearance of the epithelium, and

Kruti P Maniar *MD is a Senior Resident in Pathology at the Mount Sinai School of Medicine, New York, USA. Conflicts of interest: none declared.*

Peter Schlosshauer *MD is Assistant Professor of Pathology at the Mount Sinai School of Medicine, New York, USA. Conflicts of interest: none declared.*

characteristic "umbrella" cells.[6] Like normal urothelium, TCM expresses CK7 and (at least weakly) CK20. TCM frequently contains serotonin and calcitonin-positive endocrine cells.[7]

Although traditionally regarded as purely metaplastic, TCM has also been associated with HPV infection,[8] and with androgen-induced epithelial atrophy.[9]

Cervicitis being extremely common, **inflammatory atypia** is a very frequent finding, and must be differentiated from dysplasia. Inflammatory atypia displays an expansion of immature-appearing cells, but in contrast to HGD cell borders are well-defined, mitoses are rare without atypical forms, chromatin is finely dispersed with one or two nucleoli, and nuclear atypia is mild.

The cytologic changes of inflammatory atypia, when mild, may also mimic LGD. In such cases, the lack of clear demarcation from the normal epithelium, the absence of koilocytic atypia, and the presence of appropriate maturation favour a benign diagnosis.

Follicular cervicitis is characterized by the formation of lymphoid follicles and often associated with *Chlamydia trachomatis* infection. It may mimic HGD involving endocervical glands, especially when large, sharply circumscribed germinal centres are present containing pleomorphic cells with high mitotic activity. In such cases, the finding of tingible body macrophages (not to be confused with apoptotic cells) is a helpful diagnostic clue (Figure 1).

Useful **immunohistochemical stains** for differentiating squamous dysplasia from its benign mimics are p16, Ki-67, and ProEx C. p16 demonstrates diffuse nuclear and cytoplasmic staining in lesions associated with high-risk HPV, while it is negative in atrophy, immature squamous metaplasia, TCM, and inflammatory atypia. The Ki-67 proliferation marker is normally expressed in the parabasal cells of benign epithelium, whereas both LGD and HGD show nuclear expression in all layers of the epithelium. Although Ki-67 expression in the upper epithelial layers tends to be more intense in HGD than in LGD, this stain may not be helpful for grading.[10–12]

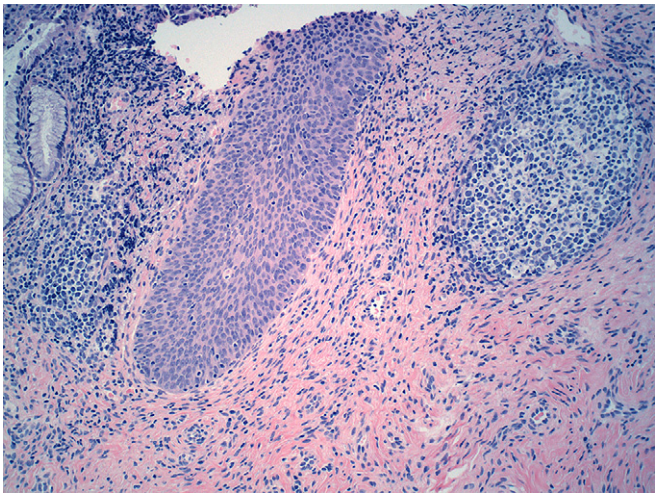

Figure 1 Follicular cervicitis. Lymphoid follicle (right) next to a focus of high-grade squamous intraepithelial lesion involving an endocervical glandular space (center). Normal endocervical glands are seen on the left. H&E, original magnification 40×. Reproduced by kind permission of World Scientific, Singapore, from: Schlosshauer P, Early diagnosis of cervical and vaginal cancer. In: Deligdisch, Altchek, eds. Early pathologic diagnosis of gynecologic cancer including a clinician's view, 2009.

ProEx C is a relatively new marker, which targets topoisomerase II-alpha and minichromosome maintenance protein-2 and indicates aberrant S-phase induction. In benign epithelium, nuclear expression is limited to the basal and parabasal layers, although upward extension within the lower half of the epithelium may be seen in immature squamous metaplasia. In contrast, dysplastic lesions show nuclear positivity in the upper layers of the epithelium. Thus, ProEx C exhibits a similar staining pattern as Ki-67, may be slightly more specific than Ki-67 for dysplastic lesions, but likewise is not ideal for grading purposes.[13,14] Combinations of these markers may increase sensitivity and specificity of the diagnosis.[15]

Mimics of invasive squamous cell carcinoma

Involvement of endocervical glands by HGD may be mistaken for invasive squamous cell carcinoma (SCC). While such foci are still confined by a well delineated basement membrane (Figure 1), features of true invasion include an irregular contour of tumour cell nests, desmoplastic stromal reaction, and a greater amount of cytoplasm in the invasive cells compared to basally located dysplastic cells ("paradoxical maturation").

When immunohistochemical stains for collagen IV or laminin are used to evaluate the integrity of the basement membrane, two caveats should be noted. Firstly, breaks in the basement membrane may be seen with marked inflammation, and do not indicate invasion in the absence of infiltrating tumour cells. Secondly, nests of invasive cells may acquire a basement membrane when not actively invading.[16]

Following biopsy, fragments of dislocated **dysplastic epithelium** may become **entrapped** within blood, fibrin or granulation tissue and be mistaken for nests of invasive tumour on subsequent excision. Clinical history and recognition of the previous biopsy site are crucial to avoid this pitfall.

During pregnancy, cervical **stromal decidualization** may occur in a very focal distribution. On the exocervix, the decidualized area may appear as a plaque or pseudopolyp. Histologically, clusters of polygonal decidualized stromal cells may be mistaken as invasive SCC. They can be distinguished based on the lack of cytologic atypia or mitotic activity (Figure 2), and the absence of cytokeratin expression. The clinical history is again crucial.

Endocervical/glandular lesions

Mimics of adenocarcinoma in-situ (AIS)

Tubo-endometrioid metaplasia is a frequent finding, in which endocervical mucinous epithelium is replaced by endometrial or Fallopian tube-type epithelium. Involved glands are usually located in the superficial third of the cervical wall. The combination of different cell types (secretory, intercalated, ciliated cells), conveying a pleomorphic appearance, with occasional mitoses, pseudostratification, branching and focal glandular crowding may mimic AIS or even invasive adenocarcinoma. The surrounding stroma may display hypercellularity or myxoid change. However, the presence of ciliated cells, bland cytology, as well as the lack of atypical mitoses or true stromal desmoplasia, helps to recognize this entity (Figure 3).