Review article

Benign mimics of cervical cancers*S Manek*

A vast number of benign lesions in the cervix are encountered in day to day practice. Many of these can mimic in situ and invasive neoplastic lesions and many precursor lesions and malignant neoplasms may mimic benign conditions. This article will describe a large number of common benign lesions and where appropriate, will discuss what these mimic. The majority of the lesions are glandular in type^(1,2). The benign lesions can be placed into five main groups of conditions. The first group does not actually include lesions but instead comprises physiological conditions. There are some lesions that cannot be readily assigned to any of these groups. The five groups are:

- 1 Physiological entities**
- 2 Metaplasias and ectopies**
- 3 Glandular hyperplasias**
- 4 Inflammatory, reactive and reparative lesions**
- 5 Benign neoplasms**

1. Physiological entities**Atrophy**

This is seen in postmenopausal or in post-natal cervixes that are devoid of oestrogen. In the former, there can be considerable crowding of nuclei with some hyperchromasia and even disarray. They can mimic high grade cervical intraepithelial neoplasia (CIN) particularly if one is considering attenuated CIN. Use of p16 and mib-1 immunohistochemistry usually helps to distinguish between the two.

Congenital transformation zone

This is found in the ectocervical portion where it can be exuberant with irregular down growths of squamous epithelial islands. The cytology is of bland cells and this is not usually a problem as a mimic of neoplasia.

Deep Nabothian cysts

This occurs in the transformation zone as a result of squamous metaplasia blocking gland outlets. The cysts can measure up to 1.5 cm in diameter and are usually visible with the

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naked eye. They are lined by a flat single layer of mucin producing endocervical epithelium. Squamous metaplasia can be seen in these cysts. They may extend deep into the stroma and hence can mimic minimal deviation adenocarcinoma (MDA). MDAs are PAX2 negative whereas a number of benign lesions including normal glands express PAX2.

Endocervicosis

This comprises glands of variable shapes and sizes which are often cystically dilated. These are lined by mucinous type of endocervical cells. They are usually present in the outer one third of the wall and can mimic MDA.

Tunnel clusters

There are two types of tunnel clusters recognised. The type A⁽³⁾ which is non-cystic, comprises of small closely packed glands often in a lobular architecture. They show pyloric gland metaplasia and are considered to be part of the spectrum of lesions showing gastric differentiation. The type B tunnel clusters are cystic and usually near the surface and not deep in the stroma. However, when they do have glands reaching deep into the stroma, they can mimic the microcystic variant of usual endocervical adenocarcinoma. Tunnel clusters also mimic MDA.

2. Metaplasias and ectopies

Transitional cell metaplasia (TCM)⁽⁴⁾

This occurs mostly in postmenopausal women and comprises epithelium which is up to and sometimes greater than 10 cells thick. It comprises disorganised, oval to spindle nuclei which are vertical in the deeper layers (Fig. 1). These nuclei may contain grooves. TCM may represent atrophic high grade CIN or may simply be a variant of atrophy. It is CK13, 17 and 18 positive (like the urothelium) and CK20 negative. It can mimic high grade CIN from which it can be distinguished by the negative staining with p16.

Immature squamous metaplasia (ISM)

This occurs within proliferation of reserve cells. There is inconspicuous intracytoplasmic glycogen. ISM is often sharply demarcated from mature squamous epithelium by a perpendicular line and can mimic high grade CIN. There is cell organisation and cohesion and no atypia (Fig. 2). Mitoses are infrequent. p16 is only patchily positive. Immature squamous metaplasia can also mimic a stratified mucinous intraepithelial lesion (SMILE) but in the latter, mucin is present throughout the full thickness of the lesion, whereas in immature squamous metaplasia, if there is any mucin present, it is usually confined to the superficial portion of the epithelium (Fig. 3).

Tubal metaplasia (TM)⁽⁵⁾

This renders epithelium similar to fallopian tube lining. There are more ciliated cells than normal together with secretory and reserve cells or intercalated cells (Fig. 4). TM can be extensive and can mimic cervical glandular intraepithelial neoplasm (CGIN). The mitotic activity is low and tubal metaplasia normally occurs near the surface. Very occasionally, the glands can show abnormal architecture and elicit a hypercellular stromal reaction. It can mimic ciliated CGIN as well as usual CGIN. Atypical tubal metaplasia has been described and this comprises enlarged and crowded nuclei, stratification and increased mitotic activity. p16 is negative in tubal metaplasia including the atypical form. There is a pseudo-infiltrative version which can mimic MDA. The latter is ER/PR negative while tubal metaplasia is positive.

Tuboendometrioid metaplasia (TEM)⁽⁶⁾

This comprises glands lined by pseudostratified epithelium composed of columnar cells with high nuclear cytoplasmic ratio. Ciliated cells or secretory cells with apical snouts are also present. There is usually no stroma around these glands. TEM occurs after surgical procedures or trauma. It can mimic CGIN. TEM is bcl-2 positive and p16 negative. CGIN is p16 and mib-1 positive and generally bcl-2 negative.

Endometriosis⁽⁷⁾

This comprises ectopic endometrial glands and stroma anywhere in the cervix but usually in the superficial one third of the wall (Fig.5). It can be cystic or may even form a circumscribed mass when in the form of an endometrioma. During pregnancy or with progesterone therapy, decidual change in the stroma may be noted. The pathogenesis of cervical endometriosis is either by implantation at surgery or trauma or true metaplasia like tubal and tubo-endometrioid metaplasia. It can mimic CGIN although the presence of stroma together with haemorrhage in endometriosis helps to distinguish it from the neoplastic process.

Atypical oxyphilic metaplasia

This is similar to eosinophilic metaplasia in the endometrium. It generally does not cause any problems with regard to mimics of neoplasia.

Epidermal metaplasias

This includes the presence of epidermis, sebaceous glands and hair follicles within the cervix. It may be a form of mesodermal metaplasia or true heterotopia.

Ectopic prostatic tissue

These are considered to derive from paraurethral Skene's glands and the ectopic

tissue is usually on the ectocervix. It comprises of a glandular component encircling squamous elements. They are usually PSA and PAP positive. They do not generally mimic any neoplasia.

3. Glandular hyperplasias

Microglandular hyperplasia (MGH)^(8,9)

This is a benign proliferation of endocervical glands and is often an incidental finding. It occurs in the reproductive age group and particularly in women who are either pregnant or are taking progesterone. It can be unifocal or multifocal and is usually polypoidal. Microscopically, it comprises small, closely packed glands with mixed inflammatory cells in the intervening stroma. MGH can be seen in endocervical polyps. The most characteristic feature of MGH is cytoplasmic vacuolation rendering a 'lace-like' pattern (Fig. 6).

It can be complicated by reserve cell hyperplasia and immature squamous metaplasia. It has a low proliferation index on mib-1 staining and is negative for bcl-2 and p16 but it can be CEA positive. Signet-ring cells can be seen or there can be marked stromal hyalinisation. There are also solid, corded or papillary forms with myxoid stroma. In some cases, hobnail cells are seen and there can be up to moderate nuclear atypia. As a result, this can mimic clear

cell carcinoma or the microglandular variant of adenocarcinoma (especially endometrial carcinoma). In the latter, the presence of stromal foam cells and vimentin positivity as well as patchy p16 positivity can help with the diagnosis of endometrial carcinoma⁽¹⁰⁾. MGH can mimic MDA and CGIN when florid and complicated by marked reactive changes.

Lobular endocervical glandular hyperplasia (LEGH)⁽¹¹⁾

This comprises tightly packed small glands showing a gastric phenotype (pyloric gland metaplasia) (Fig. 7). It presents with symptoms of abundant mucoid watery discharge. The lesion is usually confined to the inner half of the cervical wall. It tends to maintain a lobular architecture and mitoses can be seen. It is generally CEA negative. It can mimic MDA.

Diffuse laminar endocervical glandular hyperplasia (DLEGH)⁽¹²⁾

This is a rare lesion which comprises tightly packed, small to medium-sized glands present usually in the upper one third of the wall. No lobulation is seen but instead there is a sharp demarcation by a straight line between the hyperplastic glands and the underlying stroma (Fig. 8). Therefore it is not a mimic of MDA. It generally does not have any atypia. At low power it may mimic adenocarcinoma or CGIN.

Mesonephric remnants and hyperplasia⁽¹³⁾

Mesonephric remnants usually present in the lateral aspects of the cervical wall and comprise small tubules or cysts in clusters lined by low columnar, non-ciliated cells. They contain PAS positive secretions and are CEA negative. Mesonephric hyperplasia may become transmural but it retains a lobular pattern where there is a central duct surrounded by lobules of hyperplastic glands. It is a lesion usually of a young person. There may be a diffuse as opposed to a lobular version also present. Mesonephric hyperplasia can mimic MDA, CGIN and clear cell carcinoma but appropriate use of CD10 immunohistochemistry usually aids distinction from these neoplastic entities⁽¹⁴⁾.

Reserve cell hyperplasia

This is seen in the transformation zone and is common in areas of microglandular hyperplasia. It mimics CGIN or SMILE. It is generally is ER, PR cyclin-D1, bcl-2 and CD44 positive.

4. Reactive, reparative and inflammatory lesions**Reactive changes to inflammation**

These are often seen in the form of disorganised cells with nuclear atypia. The nuclei are generally uniform and there is no mitotic activity (Fig. 9). They contain prominent nucleoli. The reactive changes affect both

squamous and glandular epithelium and are often seen in ectropions. They mimic high grade or low grade CIN and also high grade CGIN.

Radiation atypia⁽¹⁵⁾

This affects both squamous and glandular epithelium and comprises nuclear enlargement with ground-glass appearance and nuclear and cytoplasmic vacuolation. There may be multinucleation and most nuclei contain multiple nucleoli (Fig.10).

Lymphoid follicles

The presence of lymphoid follicles is often associated with chlamydial infection. They do not mimic any particular neoplasia. However, any high-grade CIN present above any lymphoid follicles can be spongiotic or thin and easily overlooked (Fig. 11).

Decidual change

Can be polypoidal and mimic malignancy. It is seen in the stroma during pregnancy or affecting part of an endocervical polyp. It can microscopically mimic squamous cell carcinoma.

Arias Stella reaction⁽¹⁶⁾

This occurs in endocervical or endometriotic glands in the cervix during pregnancy. It is characterised by enlarged cells

with cytoplasmic vacuolation and irregular hyperchromatic nuclei. Hobnail protrusion is a common feature. The epithelium is usually hypersecretory. It does not form any mass lesion. Generally there is a lack of mitotic activity. The main neoplastic differentials are clear cell carcinoma (which presents as a mass) or CGIN (no vacuolation is seen in this).

Papillary endocervicitis

This is commonly seen in chronic inflammation. This comprises papillae of various sizes which are filled with inflammatory cells. This is not really a mimic unless florid when the main differential diagnosis to consider is a villoglandular adenocarcinoma.

Pseudo-invasion of benign squamous epithelium following cervical biopsy

This comprises entrapped benign squamous epithelium following loop excision or punch biopsy. It includes hypereosinophilic cells with a giant cell reaction and granulation tissue-like and inflammatory stromal response and it mimics squamous cell carcinoma.

Diathermy changes

Severe nuclear damage can be seen as a result of diathermy. This renders enlargement and hyperchromasia-like effect and can mimic

high grade CGIN, particularly when it affects glandular epithelium.

Post-operative spindle cell nodule

This is similar to that seen in the vulva or vagina. It can occur after therapeutic intervention or trauma and comprises spindle cells similar to cells seen in nodular fascitis. Many erythrocytes and neutrophils are present within the lesion

Another lesion, the inflammatory pseudo-tumour, comprises proliferation of fibroblasts, myofibroblasts and histiocytes with an inflammatory component of lymphocytes and plasma cells. There is generally no atypia or excess in mitotic activity.

5. Benign neoplasms

Endocervical polyps

These occur mainly in the 4th to 6th decades and are generally up to 2 cm in size. They can be vascular, fibrous or heavily inflamed and there is often microglandular hyperplasia. Within these polyps, there can be CIN or CGIN.

Mesodermal stromal polyps

These occur in pregnancy and are composed of oedematous stroma covered by benign squamous epithelium. The cells in the stroma are bland and occasionally include bizarre cells. These are vimentin and alpha 1

anti-chymotrypsin positive. The main mimic is of sarcoma botryoides.

Placental site trophoblastic nodule

This can occur in the endocervix and is similar to that in the uterus. It comprises hyalinised stroma with intermediate trophoblasts and inflammatory cells. The trophoblasts can be degenerate. There is a lack of mitoses and significant nuclear atypia. These stain positively with HPL. They can mimic squamous cell carcinoma.

Mullerian papilloma

This is a benign papillary growth seen in children. It is made up of complex papillary projections lined by flat cuboidal epithelium with cores of loose fibrovascular tissue. There is generally no atypia or excess mitotic activity.

Adenomyoma⁽¹⁷⁾

This comprises fibrous and muscular stroma intermingled with large and small endocervical glands in a lobular pattern. There is generally no atypia seen, nor any features of invasion or mitotic activity. It can mimic adenocarcinoma if florid.

Papillary adenofibroma

This is a rare lesion comprising endocervical or tubal glands surrounded by stroma which is fibrous and forming broad

papillary projections or outlines (Fig.12). They can mimic villoglandular adenocarcinoma but more importantly an adenosarcoma and particular attention needs to be paid to the stromal component.

Squamous papilloma

These are similar to fibroepithelial stromal polyps and do not show any HPV association. If florid, it can mimic the papillary variant of squamous carcinoma

Condyloma acuminatum

These may present as large polypoid or papillary lesions. These are usually HPV driven and may be complicated by CIN. The immature type can mimic papillary squamous carcinoma.

In conclusion, one has to remember that there are a vast number of benign conditions in the cervix compared to other areas of the female genital tract. Most of these are easily recognised and do not cause any diagnostic problems. However, some lesions may mimic neoplasms for which particular attention to morphology is required and the use of immunohistochemistry may be helpful. A comprehensive list of lesions is tabulated for ease of reference (Tables 1-4). Some of these lesions have not been discussed in this article.

Table 1. Mimics of cervical squamous intra-epithelial neoplasia

Low grade CIN	High grade CIN
<ul style="list-style-type: none"> • Immature metaplasia • Atrophy • Reactive and inflammatory changes • Radiation atypia • Diathermy changes • Various other artefacts – signet ring degeneration, artefact induced by Lugol's iodine, etc 	<ul style="list-style-type: none"> • Immature metaplasia • Atrophy • Transitional cell metaplasia • Specific changes over lymphoid follicles • Nodular aggregates of histiocytes in endometrial samples

Table 2. Mimics of cervical glandular intra-epithelial neoplasia/SMILE

<ul style="list-style-type: none"> • Immature metaplasia (SMILE mimic) • Tubal Metaplasia • Endometrioid metaplasia • Tuboendometrioid metaplasia • Endometriosis • Microglandular hyperplasia • Diffuse laminar endocervical glandular hyperplasia • Mesonephric hyperplasia 	<ul style="list-style-type: none"> • Reserve cell hyperplasia • Reactive and inflammatory changes • Arias Stella reaction • Papillary endocervicitis • Mullerian papilloma • Diathermy changes • Overstaining artefact
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Table 3. Mimics of cervical squamous carcinoma

<ul style="list-style-type: none"> • Florid squamous metaplasia involving many glands • Decidual reaction • Placental site trophoblastic nodules • Pseudoinvasion of benign squamous epithelium following surgical procedures • Congenital transformation zone <p>Squamous papilloma (mimic of papillary squamo-transitional carcinoma)</p> <p>Immature condyloma (mimic of papillary squamous carcinoma)</p>
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Table 4. Mimics of cervical adenocarcinoma

- Deep Nabothian cysts and/or endocervical glands (MDA)
- Endocervicosis (MDA)
- Tunnel clusters (MDA and/or microcystic variant of usual carcinoma)
- Florid endometriosis
- Microglandular hyperplasia (clear cell carcinoma, MDA and microglandular variant of endometrial adenocarcinoma)
- Lobular endocervical glandular hyperplasia (MDA)
- Diffuse laminar endocervical glandular hyperplasia (usual type adenocarcinoma)
- Mesonephric remnants or hyperplasia (mesonephric carcinoma, MDA, clear cell carcinoma)
- Arias Stella reaction (clear cell carcinoma)
- Florid adenomyomatosis (usual adenocarcinoma)
- Papillary adenofibroma (adenosarcoma or villoglandular carcinoma)
- Papillary endocervicitis (villoglandular carcinoma)
- Mullerian papilloma (villoglandular carcinoma)
- Nodular clustering of endocervical glands (MDA)
- Pseudoepitheliomatous hyperplasia of glands with inflammation (adenoid basal carcinoma)
- Endocervical polyps (sarcoma botryoides)
- Degenerate endocervical cells (signet ring adenocarcinoma)
- Mesodermal stromal polyps (sarcoma botryoides)

Fig.1

Fig.1. Low power image of transitional cell metaplasia. The appearance at this magnification is similar to high grade CIN. Higher power examination would show nuclear grooves in otherwise bland nuclei.

Fig.2

Fig.2: Immature squamous metaplasia. In this figure only part of one gland has undergone metaplastic change. Note the regular, aligned nuclei and the lack of pleomorphism and mitotic activity. When florid, this can mimic high grade in situ squamous neoplasia.

Fig.3a **Fig.3b**

Fig. 3. (a) Immature and mature squamous metaplasia with residual glandular epithelium confined to the most superficial portion of the epithelium. In contrast, a SMILE lesion would contain mucin throughout the full thickness of the epithelium **(b)**.

Fig.4

Fig. 4. Part of a gland lined by tubal type of epithelium with abundant ciliated cells. There is no atypia.

Fig.5

Fig.5. Cervical tissue with endometriosis. Note the haemorrhage around the glands. In this case, some of the endometriosis reaches the surface and may appear abnormal on colposcopy.

Fig.6

Fig. 6. High power view of an area of microglandular hyperplasia showing closely packed glands with a lace like pattern and the presence of many neutrophil polymorphs. Occasional mitotic figures are apparent. This can mimic adenocarcinoma of both endocervical and endometrial type.

Fig.7

Fig.7. Glandular hyperplasia in a lobular fashion with a central duct and surrounding glands. The overall morphology is of gastric type differentiation. This can mimic gastric type adenocarcinoma.

Fig.8

Fig. 8. Glandular hyperplasia in a laminar fashion with a sharp demarcation between the hyperplastic glands and the underlying stroma. This can mimic adenocarcinoma

Fig.9

Fig. 9. Reactive atypia. The nuclei are slightly atypical on a background of inflammation. There is slight disarray of the cells with papillae formation. No mitotic activity is seen in this field.

Fig.10

Fig. 10. Radiation atypia with significant nuclear changes including a 'glassy' appearance, vacuolation and the presence of prominent nucleoli. These changes can mimic in situ neoplasia.

Fig.11a **Fig.11b**

Fig.11. (a) Prominent lymphoid follicle with spongiotic high grade CIN overlying the follicle. This CIN can be easily overlooked but can be confirmed using p16 immunohistochemistry **(b)**.

Fig.12

Fig. 12. Low power view of a papillary adenofibroma. Note the frond-like peripheral architecture. The deeper glands can become quite distorted, rendering an appearance of staghorn glands which are commonly seen in adenosarcomas.

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