Infections in the gynaecological tract

Sanjiv Manek
Sunanda Dhar

Abstract

In the context of infections in the body, those that occur in the gynaecological tract are less common and perhaps less clinically significant compared with other body sites. However, a few infections are important in view of their association with pathological sequelae such as tumour formation or pelvic inflammatory disease complex. This review will discuss some of the most relevant infections, first under histology, which will be further subdivided into locations in the genital tract and then under cytology, which focuses mainly on the infections seen in cervical cytology samples. There will be only brief mention of the less common infections or those that do not produce diagnostic challenges or lead to significant complications.

Keywords cervical screening; HPV; HPV-ISH; HSV; p16 immunohistochemistry; pelvic inflammatory disease; tumourigenesis

Introduction

In the gynaecological tract, particularly in the lower part, infections are not uncommon. In this region, most are sexually transmitted and can occur in both the immunocompetent as well as the immunocompromised. In the latter group, however, some of the infections are more prevalent and complications arising from them perhaps more significant. Most of the infections are symptomatic and result in both specific and non-specific histological features. Some have advanced local effects, such as pelvic inflammatory disease, whilst a few can cause systemic complications. A few, such as the human papilloma virus are associated with tumourigenesis.[1]

Histology

Vulva

The important infections in the vulva are those caused by the human papilloma virus (HPV).[2] The lesion associated with HPV infection is the condyloma acuminatum or wart and is usually caused by the low risk HPV subtypes such as 6 or 11. The condylomas occur mainly on the medial aspect and can vary in size. These can be ablated or surgically removed. They can increase in size and number during pregnancy but can also regress following pregnancy. A few that contain high risk HPV types are regarded as pre-cancerous and usually show a picture of high grade VIN (warty type). Most condylomas, however, being due to low risk HPV show no more than VIN 1. Histologically, condylomas are papillomatous and/or branching with acanthotic surface squamous epithelium that can proliferate endophytically. Typical koilocytes are seen in the superficial layers where they stain positively with mib 1/ki-67 and p16. At the base of the squamous epithelium, there may be crowding of nuclei indicating parabasal hyperplasia. At the very top of the epithelium, there may be para- and/or hyperkeratosis. Condylomas can rarely be flat or seborrhoeic keratosis-like and may occasionally show pseudobowenoid change.

Classical VIN[3] is high grade dysplasia and is usually subdivided into basaloid and warty, although most are mixed.[3] In the warty VIN, there are obvious changes of HPV infection evident, including koilocytosis, dyskeratosis and multinucleation and there is strong, diffuse staining with p16. In the basaloid variant, koilocytosis may rarely be seen. In 50% of women who have HPV-related VIN, there is associated cervical intraepithelial neoplasia (CIN).

Herpes simplex virus (HSV) infections are not uncommonly found in the vulva and the majority are due to HSV type 2.[4] Infection of the vulva or vagina with HSV 1 may occur in childhood or early adolescence but the more common HSV 2 infection occurs after puberty and sexual activity. Incidence of HSV infection in the UK has been increasing in the last few decades and HSV 2 is a risk factor for concurrent or subsequent HIV infection. An uncommon anogenital HSV infection in immunocompromised patients is hypertrophic herpes simplex genitalis.[5] HSV infection can be asymptomatic but more commonly, there are symptoms which include localized pain, inguinal lymphadenopathy and there may be systemic symptoms such as fever and malaise. On the vulval skin, HSV infection manifests as vesicles, which usually rupture, pustules and ulcers. Histology of the skin around these lesions shows multinucleate cells with typical ground glass nuclei with intranuclear eosinophilic inclusions. There is often considerable deformation of the epidermis (Figure 1) and dermis and as part of the healing process, pseudoepitheliomatous hyperplasia can be seen in adjacent skin. Erythema multiforme-like features may also be seen. At its extreme, the morphological changes can mimic invasive, well-differentiated squamous carcinoma. It is very important to be alert to the possibility of HSV infection in such cases, particularly when there is considerable disruption of the epidermis. It is possible to stain immunohistochemically for HSV 2.

Other viral infections include cytomegalovirus (CMV) which can cause similar disruptive changes as HSV infection. These tend to occur in immunocompromised women. Infection with molluscum contagiosum is also seen in the vulva. Human immunodeficiency virus (HIV) infection itself can cause ulceration.

Other infections that occur in the vulva, but are not commonly a diagnostic challenge nowadays, are: syphilis (seen as chancres, rash and papules) caused by the spirochaete *Treponema pallidum*; granuloma inguinale (seen as papules and ulcers and subsequent abscesses) caused by *Calymmatobacterium granulomatis*; lymphogranuloma venereum (seen as ulcers and painful inguinal lymphadenopathy) caused by *Chlamydia trachomatis*; tuberculosis (seen as ulcers or as mass lesions); and necrotizing fasciitis and Bartholin's gland infection by *Neisseria gonorrhoeae* and *C. trachomatis*. Most often, the diagnosis is

Sanjiv Manek *FRCPath Consultant Gynaecological Pathologist, Oxford University Hospitals, Oxford, UK. Conflicts of interest: none declared.*

Sunanda Dhar *FRCPath Consultant Gynaecological Pathologist, Oxford University Hospitals, Oxford, UK. Conflicts of interest: none declared.*

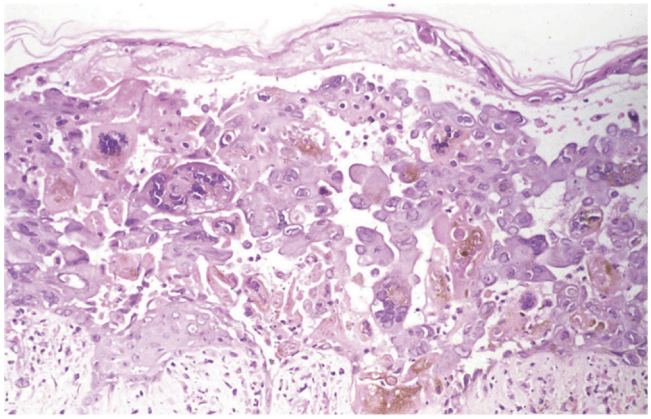

Figure 1 Vulval HSV infection with marked distortion of squamous epithelium. HSV is seen as multinucleated cells with ground glass nuclei. H&E _40.

made clinically and by microbiological cultures as the histological features are not always specific. Many of the above infections occur increasingly in immunocompromised women, particularly those who are infected with HIV. Diabetes is associated with some bacterial infections.

Fungal infections such as with *Candida albicans* can be chronic. The histology associated with these infections is nonspecific. Very occasionally, periodic acid Schiff (PAS) stains will be able to demonstrate hyphae and spores in the inflammatory infiltrates. It is common practice to use this stain in nonspecific inflammatory conditions. Parasitic infections include schistosomiasis and enterobiasis. The histology with these is also non-specific, although florid reparative changes in adjacent skin can mimic invasive neoplasia.

Vagina

All of the above infections can also be found in the vagina. They are associated with various symptoms such as discharge, dryness, dyspareunia and post-coital bleeding. The histological changes are non-specific. Candidal infection in the vagina is often identified on cervical cytology. When severe, it can cause marked reactive changes in the basal part of the surface squamous epithelium rendering features of low grade vaginal intraepithelial neoplasia (VaIN). HPV infection is associated with neoplasia and there is a high incidence of concurrent cervical and vulval HPV infection and CIN/VIN.

One diagnostic challenge sometimes encountered is in differentiating glycogen-rich superficial cells from those infected by HPV. Koilocytes typically have a sharp halo around a damaged nucleus. The koilocytic nuclear damage includes pyknosis and severe wrinkling (Figure 2). In glycogenated cells, the clearing around a normal nucleus is ill-defined.

Cervix

Infections in the cervix are usually noted in cytology samples (discussed later). Histologically, it is difficult to identify infections such as candidiasis and there are generally no specific features. HPV infection is by far the commonest and most important because of its association with CIN and cervical glandular intraepithelial neoplasm (CGIN) and the subsequent

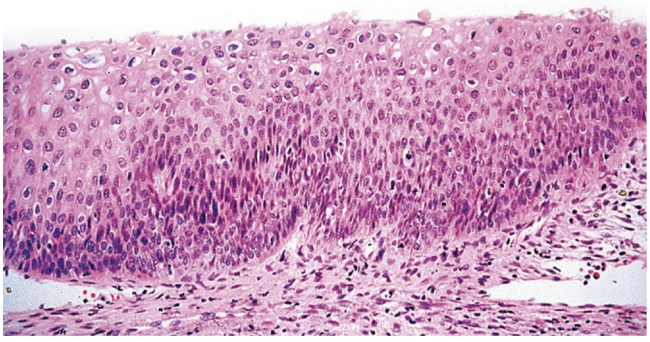

Figure 2 Vaginal squamous epithelium showing koilocytosis and intraepithelial neoplasia, grade 1–2. H&E _40.

progression, in untreated cases, to invasive squamous carcinoma or adenocarcinoma, respectively.[6] HPV infection can cause condylomas (low grade lesions) and flat CIN (high grade lesions). In low grade CIN, the pathognomonic koilocytic atypia is readily apparent but in high grade CIN, the koilocytes are difficult to find, usually compressed to the topmost layers of the surface epithelium. Other associated changes include basal cell crowding, multinucleation, dyskeratosis and parakeratosis. HPV infection in glandular epithelium is difficult to identify, but usually manifests as multinucleate forms. HPV associated neoplasia is p16 positive, which is reliably used nowadays to identify subtle CIN/CGIN in contrast to immature metaplasia in squamous epithelium and tubo-endometrioid metaplasia in glandular epithelium.[7] Nowadays, it is possible to perform HPV-in situ hybridisation immunohistochemistry (HPV-ISH) to demonstrate HPV related neoplasia.[8] This is useful in malignancies detected elsewhere when a cervical primary malignancy related to HPV is suspected (Figure 3).

Other viral infections include CMV cervicitis, usually in the immunocompromised patient, with the characteristic inclusions found in endocervical, endothelial or stromal cells. There may be lymphoid follicles in the vicinity.

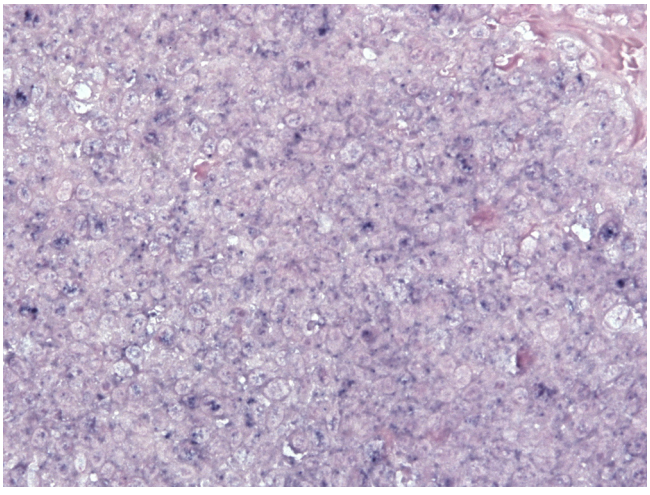

Figure 3 Use of HPV-ISH to demonstrate the presence of HPV in malignancies. The positivity is indicated by faint blue speckling.