tumour cells with clear to pale eosinophilic cytoplasm mimicking the intermediate cells of MEC. Thyroid sclerosing mucoepidermoid carcinoma with eosinophilia is a unique histological variant of MEC with tumour cells arranged in nests and anastomosing cords, keratinisation, cysts lined by mucous/goblet cells, a fibrohyaline stroma with eosinophils, and negative for *MAML2* rearrangements.[7] The most reliable histological finding is that CCC lacks mucous cell-lined cysts, an important feature of thyroid MEC and thyroid sclerosing MEC with eosinophilia. SqCC and CCC have similar immunohistochemical phenotypes because both tumours are positive for p63 and negative for thyroid gland markers. However, primary thyroid SqCC is a high-grade malignancy typically associated with marked cellular pleomorphism and keratinisation. CCC shows low-grade cytological features and no keratinisation. It is important to use molecular or cytogenetic methods to demonstrate *EWSR1* rearrangement to confirm the diagnosis. A secondary tumour from a primary salivary gland CCC is a very important differential diagnosis. Since CCC is a low-grade salivary gland malignancy, distant metastasis is usually found after the operation of the primary tumour after years during follow-up.[1,4,9,10] In this case, a primary thyroid CCC is considered because the patient had no surgical history and no other lesions could be found by full-body CT scans.

Due to its rarity, the prognosis of primary thyroid CCC is not clear. Long term follow-up is needed as delayed recurrence or distant metastases have been reported in patients with primary tongue base or pulmonary CCC.[4,9,10]

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Histopathological evaluation of colposcopic biopsies, LLETZ and cold knife cone biopsies of the uterine cervix in post-menopausal women: considerations in the setting of the new Australian cervical HPV DNA screening program

Sir,

The Australian Renewed National Cervical Cancer Screening Program (RNCSP) commenced on 1 December 2017 after several years of thorough planning by several committees of experts, and acceptance of their recommendations by the Medical Services Advisory Committee (MSAC).[1] The RNCSP represents a quantum shift in the approach to cervical cancer screening and was predicated by the introduction in 2007 of the extremely successful Australian National HPV Vaccination Program (NHVP).[2] After the introduction of the NHVP, reduction in the incidence of precursor lesions of cervical cancer in vaccinated women has been reported,[3] and a recent publication[4] predicts that the incidence of cervical cancer in Australia will fall to less than 4 per 100,000 women by the year 2034.

A cervical screening test (CST) in the RNSCP[1] requires cervical brushings to be submitted in liquid-based cytology fixative for human papillomavirus (HPV) DNA testing for most but not all known HPV types associated with the pathogenesis of cervical cancer. The HPV DNA testing is by partial genotyping for HPV-16, HPV-18 (HPV-45 typing optional) and HPV other types (non-16/18). The RNSCP provides guidelines for pathologists reporting CST.[1] Those specimens found to be HPV DNA positive are submitted for reflex liquid-based cytological evaluation (LBC) and appropriate management of the patient is recommended in a combined HPV DNA and LBC report. Patients with 'high-risk' HPV types 16 and 18 are recommended for referral for colposcopy regardless of the LBC findings. Patients with brushings positive for HPV non-16/18 are triaged upon LBC findings. A patient with a high grade intraepithelial lesion (HSIL) or possible HSIL is recommended for referral to colposcopy, while a patient with a low grade intraepithelial lesion (LSIL) or possible LSIL, or no intraepithelial lesion (NIL) is recommended to undergo repeat testing in 12 months. Patients whose brushings are negative for HPV DNA are recommended to be recalled for HPV DNA testing in 60 months. Those patients who have not had previous cervical screening or in patients over the age of 35 whose brushings are found to be HPV DNA positive are recommended to be referred for colposcopy. There has been a cohort of patients being followed up for positive cytology screening tests prior to introduction of the HPV DNA screening program.

The roll-out of the RNCSP includes recommendations to gynaecologists[5] for the follow-up and management of patients whose cervical brushings are shown to have an HPV infection by HPV DNA testing. Guidelines for the colposcopic evaluation of women whose brushings are HPV DNA positive have been promulgated[5] and the Australian Society of Colposcopy and Cervical Pathology (ASCCP) has promoted improved training and colposcopic techniques.[6] In patients whose transformation zone is partially visualised (TZ type 2) or not visualised at all (TZ type 3) cone biopsy or endocervical curettage for pathological assessment is recommended.[5] This letter discusses observations by the author regarding the colposcopic biopsies, large loop excision of the transformation zone (LLETZ) and cold knife cone biopsies on post-menopausal women received during the first year of the screening program at a laboratory in Wollongong, New South Wales.

Perhaps the most important observation has been the increase in numbers of post-menopausal women coming to colposcopy as a result of a positive HPV DNA screening test. This observation is anecdotal and meaningful statistical analysis of numbers in this small laboratory is not feasible. The first analysis of records in the National Cervical Screening Register is awaited with interest. However, at the present time, this observation deserves discussion for several reasons. Firstly, many women (and sometimes their physicians) express surprise at being told they have evidence of an HPV infection. In some cases their previous Papanicolaou smear(s) (Pap test) were negative. Many patients (and sometimes their physicians) are under the impression that since they have been in longstanding monogamous sexual partnerships, or are no longer sexually active, that they could

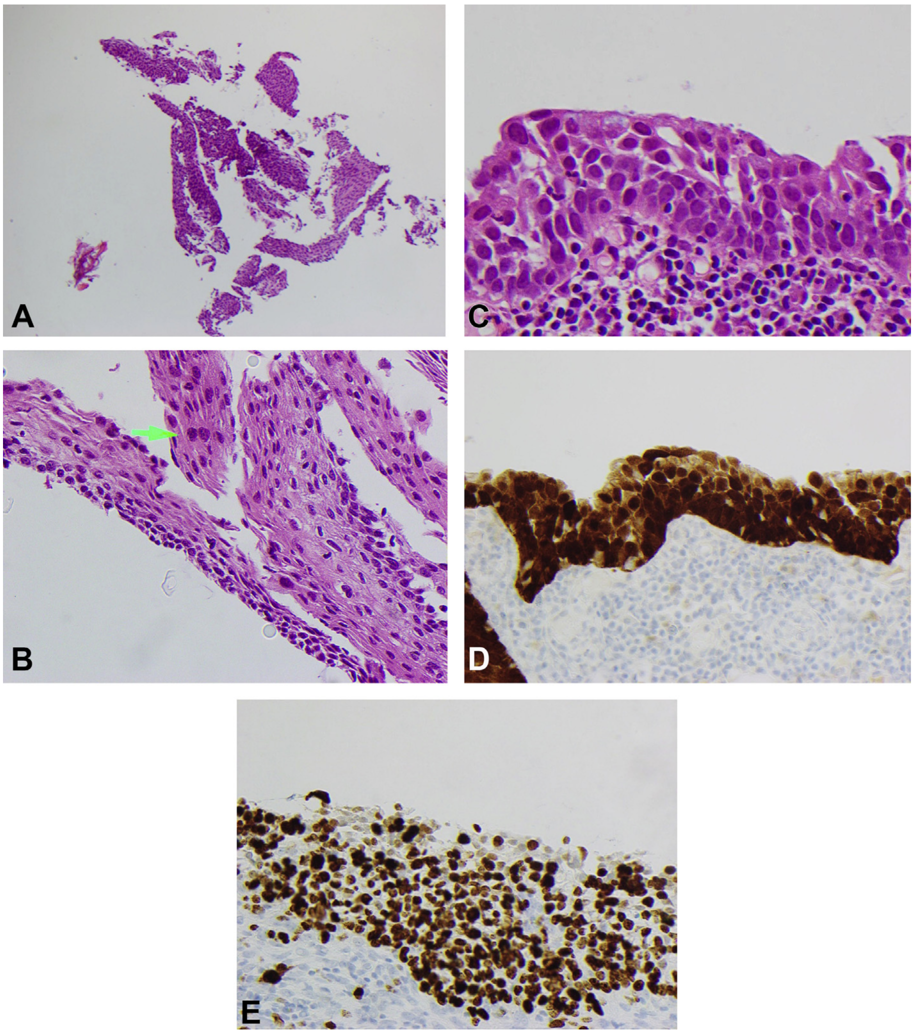

Fig. 1 (A) Stripped atrophic cervical epithelium in a LLETZ of cervix. (B) Stripped atrophic cervical epithelium in a LLETZ of cervix showing subtle changes consistent with HPV effect (LSIL, WHO 2014). (C) Atrophic squamous epithelium showing atypia that may appear questionable for a high grade intraepithelial lesion (HSIL, WHO 2014) on H&E stained sections. (D) The same atrophic squamous epithelium as in C, showing *en bloc* p16 positive staining confirming a HSIL. (E) The same atrophic squamous epithelium as in C, showing Mib-1 nuclear staining confirming a HSIL.

not possibly have an HPV infection. The concept of long-standing latent HPV infection has been put forward[7] and may offer an explanation that the patient and physician will accept. On occasion, the reflex LBC does not identify an intraepithelial lesion which may contribute to confusion in the mind of both patient and physician.

As might be expected, many post-menopausal patients exhibit atrophic changes in the cervical epithelium and this may explain an apparently negative LBC in the face of a positive HPV DNA test. The evaluation of atrophic cervical Pap tests and LBC can be challenging[8] and subtle changes of HPV infection might be missed. For this reason, for many years, a course of vaginal oestrogen cream has been recommended and effectively used to alleviate the problem of evaluating an atrophic cervix by Pap test.[8] Ideally, use of the cream should be prescribed for at least two applications per week for 6 weeks after the problematic smear. A repeat Pap test or LBC should be taken 10 days after completion of the course. Similarly, the use of oestrogen cream in women in low oestrogen states, applied twice weekly for 6 weeks prior to colposcopic evaluation has been reported to improve both the rate of satisfactory colposcopies and the accuracy of prediction of high grade lesions in the colposcopic biopsy.[9] On the other hand, since latent HPV infection is not well characterised or understood,[7] it is possible to conceive that there may be no recognisable viral cytopathological effect despite the detection of HPV DNA in squamous and mucinous endocervical cells.

As a consulting pathologist, I have had discussions with several gynaecologists who experience uncertainty whilst managing post-menopausal women who have an unexpected positive HPV DNA test and are required to undergo colposcopy. On many occasions no lesion has been seen at colposcopy and frequently colposcopy showed a type 2 or type 3 TZ. Following the RCSNP recommendations,[5] a follow-up repeat CST and colposcopy occurs, and frequently the gynaecologist is still unable to visualise a lesion, and will submit an endocervical curettage specimen or a cone biopsy for histology. Since the atrophic epithelium is extremely friable it may strip easily from the LLETZ or cone biopsy (Fig. 1A,B) and extremely careful handling of the specimen both in the colposcopy suite and at the pathology cut-up bench is vital. Undue handling and manipulation of the specimen while inking resection margins can be problematic. Since cautery artefact at the margin is obvious in sections from a LLETZ, the inking step can safely be omitted when dissecting these specimens. Added to the problem of stripped epithelium in these specimens, the morphological cytopathological effect of HPV is sometimes very subtle in atrophic epithelium[8] (Fig. 1B,C). The use of p16 immunohistochemical (IHC) staining can reveal when least expected the typical *en bloc* positive staining (Fig. 1D), and with Mib-1 positive nuclei (Fig. 1E) in the basal layer and at least the lower third of the epithelium described in the lower anogenital squamous terminology (LAST) criteria.[10] Although the LAST recommendations suggest that a morphological low grade appearance should trump an apparently positive p16 staining pattern, the author believes that in atrophic epithelium it may be more accurate to give precedence to the IHC findings and that a positive p16 stain with appropriate Mib-1 staining should prevail in the diagnostic process. Cone biopsies in post-menopausal women may show immature squamous metaplasia, and more than one separate isolated HSIL or LSIL, all of which may require p16 staining to be fully evaluated. Cases have been seen in which a diagnosis of HSIL may have been missed if only one of the sections being evaluated was submitted for p16 IHC.

One of the more interesting and pleasing findings in colposcopic specimens taken from women with positive HPV DNA CST is the increased numbers of patients showing adenocarcinoma *in situ* (AIS) (Fig. 2). In those AIS cases seen to date, all have stained positively for p16 by IHC, although it is to be expected that 'gastric-type' AIS would not be p16 positive.[11] Again, these observations concerning AIS are anecdotal and numbers of cases are too few for statistical analysis at present.

In reporting cervical pathology in colposcopic biopsies, pathologists are participating in the quality assurance measures[5] that are to be applied to gynaecologists practising colposcopy. Therefore, it is imperative that a minimum amount of important information should be provided by the gynaecologist on the histology request form, including the full CST findings, the appearance of the cervix, the presence of aceto-white areas, mosaicism, increased vascularity and whether the transformation zone was visualised (i.e., type 1, 2 or 3 TZ). This information will assist the pathologist in evaluating the biopsy specimen, allowing a more comprehensive report. Further, the pathologist should report accurately on a number of parameters that may not have been traditionally included in colposcopic biopsy pathology reports in the past. Included in the pathology report should be the presence or absence of LSIL (including HPV effect),

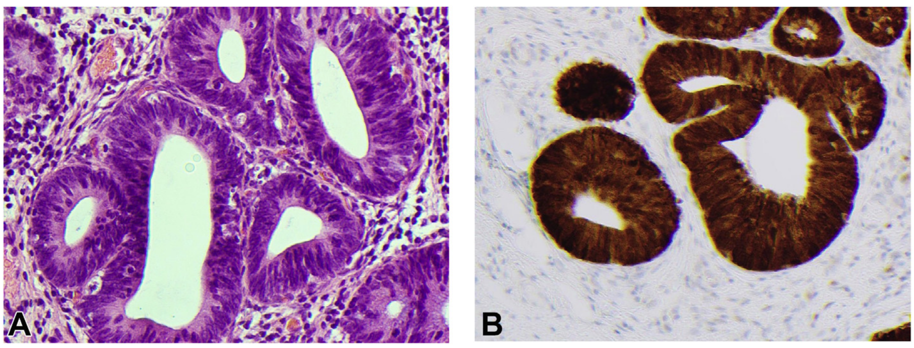

Fig. 2 (A) LLETZ showing adenocarcinoma *in situ* (AIS WHO 2014) and (B) showing strong positive staining for p16.

Delete all that do not apply:

Cervix, colposcopic biopsy/LLETZ/cone biopsy:

Diagnosis:	NIL (No intraepithelial lesion WHO 2014) LSIL (CIN 1 with HPV effect WHO 2014) HSIL (CIN2/3 WHO 2014) Squamous cell carcinoma Immature squamous metaplasia Adenocarcinoma in situ (AIS, HGGA) Adenocarcinoma Atrophic change
Extending into crypts:	Not / Identified
Epithelial stripping:	Not / Present
Invasive disease:	Not / Identified / Micro-invasive
Depth of invasion:	mm
Transformation zone:	Not / Represented
Margins:	
Ectocervical:	Not / Clear
Endocervical:	Not / Clear
Circumferential:	Not / Clear
p16 status:	Negative / Positive

Fig. 3 A proposed synoptic reporting format for pathologists reporting colposcopic biopsies and cone biopsies or LLETZ.

HSIL, AIS, micro-invasive or more advanced invasive disease.[12] Additional information about the presence of immature squamous metaplasia, atrophy of epithelium, and stripping of epithelium may explain, for example, an unexpected finding of no intra-epithelial lesion (NIL). A synoptic report as an *aide memoire* for the pathologist and a format to summarise these important components of the pathology report may be useful, can include information about the surgical margins in a cone or LLETZ biopsy, and the p16 status if tested (Fig. 3).

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Primary immature teratoma of the thigh

Sir,

Teratomas are germ cell tumours composed of a variety of somatic tissues derived from more than one germ layer (ectoderm, endoderm and mesoderm), commonly found in the gonads, in children and young adults.[1] Less frequently teratomas arise in extragonadal sites, usually in a midline location, such as sacrococcygeal region, retroperitoneum, mediastinum and central nervous system. Mature teratomas harbour, by definition, mature, benign, well-differentiated tissues, while immature teratomas are composed of variable amounts of fetal, immature tissues. Monodermal teratomas are defined by the presence of a single tissue type (i.e., thyroid tissue in struma ovarii). Usually, immature teratomas are graded according to the Norris grading system,[2] based on the presence and amount of immature neuroepithelial component. Both mature and immature teratomas may contain foci of other germ cell tumours, as well as foci of malignant transformation. We report the very unusual case of a primary immature teratoma arising in left thigh soft tissue in an elderly woman.

An 86-year-old female presented with an ulcerated soft tissue mass in the postero-inferior region of the left thigh. The resected lesion, measuring 14 × 13 × 4.5 cm, appeared soft, brownish and multilobulated on the surface. After sectioning, the mass showed both solid and cystic-like areas containing a mucoid material; necrosis and haemorrhages were also present. Histological examination revealed a neoplasm with both mesenchymal and epithelial differentiation. Areas with tubular and glandular structures, reminiscent of embryonic tissues, embedded in a cellular stroma, were frequently observed (Fig. 1A,B). Cystic spaces lined by a prismatic or cubic epithelium were also present. Primitive MAP2+/CD56+ neuroepithelium arranged in tubules and rosettes, with brisk mitotic activity, admixed with mature glial (GFAP+) and meningeal tissue, was frequently detected (Fig. 1C). A scarce mesenchymal component was also present, prevalently consisting of mature cartilage islands (Fig. 1D) and well differentiated smooth muscle fibres, without overt features of malignancy. Infiltration of soft tissues at the periphery of the lesion was focally observed. In the specimens examined, there was no evidence of residual ovarian tissue. The above morphological features led to a