



Figure 1. Examples of CAIX immunohistochemical staining in AIS and CIN III of the cervix uteri: moderate diffuse overexpression in AIS (A), and patchy CAIX expression in apical layers of the dysplastic squamous epithelium in CIN III (B).

In summary, CAIX is overexpressed in the vast majority of cervical AIS cases, and may be a helpful additional diagnostic marker for the detection of atypical glandular lesions in both cervical biopsies and cytological specimens.

CONFLICT OF INTERESTS

The authors confirm that there are no conflicts of interest.

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Virtual microscopy is a valid alternative for the diagnostic assessment of laryngeal premalignancies

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Sir: Whole slide imaging (WSI) is a technology in which histopathological slides are optically scanned to produce digital images. Among the advantages of WSI in surgical pathology are the possibilities of remote diagnosis and of fast retrieval of archival specimens. Controversy still remains over whether WSI is a valid alternative to the traditional light microscope for diagnosis. Numerous validation studies have been published, and have generally shown good correspondence between these two modalities.¹ The College of American Pathologists recently released guidelines supporting the implementation of WSI for diagnostic

purposes.² We performed a study to validate WSI for preneoplastic lesions in laryngeal biopsies. We previously showed that the diagnosis of such lesions is inherently difficult, resulting in limited observer reproducibility.³ The option of remote consultation of these lesions may be of benefit in laryngeal histopathology. However, because subtle differences can have major clinical implications, validation of WSI for this purpose is necessary. Our study complies with the guideline mentioned above.²

Sections from a previously reported series of laryngeal biopsies³ ($n = 110$) were scanned using an Olympus dotSlide system ($\times 40$ objective). Three pathologists with head and neck pathology as a field of interest reviewed these cases, using WSI and a calibrated monitor, according to the 2005 WHO classification system.⁴ The reproducibility of the full WHO system is poor, and may be improved by using a system that more closely complies with diagnostic patient management.³ In this study, the WHO system was converted into a three-grade system: 26 cases 'within normal limits' (normal, hyperkeratosis, inflammation, and hyperplasia); 55 cases 'requiring close monitoring' (mild and moderate dysplasia); and 29 cases 'prompting immediate treatment' (severe dysplasia and CIS). A consensus diagnosis was reached for 83 cases using glass slides³: either the initial diagnosis was concordant for all three pathologists, or they reached agreement during a consensus meeting. Concordance rates were calculated as the proportions of agreement with the consensus diagnosis. Kappa statistics were calculated to study the level

of agreement between different (glass slide and WSI) readings.

In general, WSI assessment of laryngeal premalignancies showed interobserver agreement comparable to that obtained with glass slides (Table 1). The intraobserver (glass slide versus WSI) agreement (average kappa of 0.45) was generally better than the interobserver agreements for WSI and glass slide diagnoses. Concordance for different pathologists with the consensus diagnoses was, in general, lower for WSI than for glass slide diagnoses, the difference exceeding 10% for all three pathologists. None of these differences reached statistical significance (Fisher's exact test, $P > 0.05$). If we consider only the differentiation between severe dysplasia and worse (cases 'prompting immediate treatment') versus all other cases, on average the concordance rates for glass slide and WSI diagnoses increase to 89% and 84%, respectively (data not shown). For each pathologist, the full WHO grading was compared between WSI and glass slides to detect possible overdiagnosis or underdiagnosis caused by the use of WSI. No systematic biases could be shown from the data in the present study (signs test, $P > 0.05$).

This study shows that observer agreement is comparable for glass slide and WSI diagnoses for laryngeal biopsies. Apparently, observer variability is not caused by the imaging modality, but rather by the lack of objective and reproducible criteria presently in use for grading laryngeal dysplasia. For different pathologists, grading into the three clinically relevant classes showed discordance with the consensus

Table 1. Overview of results of assessment of larynx preneoplasia

| | Glass slides* | WSI |
|--|------------------|------------------|
| Observer variability (Kappa values with 95%CI) | | |
| Overall interobserver | 0.39 (0.31–0.47) | 0.38 (0.30–0.46) |
| Average intraobserver (glass slide vs WSI) | | |
| Pathologist 1 | | 0.48 (0.34–0.63) |
| Pathologist 2 | | 0.41 (0.27–0.55) |
| Pathologist 3 | | 0.45 (0.31–0.59) |
| Concordance with consensus diagnosis | | |
| Pathologist 1 | 70/83 (84%) | 56/78 (72%) |
| Pathologist 2 | 61/83 (73%) | 52/83 (63%) |
| Pathologist 3 | 67/83 (81%) | 53/78 (68%) |

*Taken from Fleskens *et al.*³

diagnosis in 16–27% of cases, resulting in one in five patients being given a histopathological grade different from the consensus (gold) standard. This problem may be alleviated by having multiple pathologists assess difficult cases, which can easily be done using WSI. The results of the present study show that alternative WSI-based assessment of laryngeal premalignancies will not compromise diagnostic accuracy.

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Cap polyposis and colitis cystica profunda: a rare association

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Sir: Cap polyposis and colitis cystica profunda (CCP) are two rare, benign and distinct colorectal conditions whose aetiology remains unclear. A rare association

between cap polyposis and CCP has already been described; in those cases, cystic glands were present in the submucosal layer of the cap polyps.^{1,2} Interestingly, in the present case, lesions of CCP were not intermingled with cap polyps, but were distant from them.

A 49-year-old man with chronic colitis located in the left colon and rectum, diagnosed as ulcerative colitis 5 years previously, was referred to our institution for persistent mucous bloody stools refractory to immunosuppressive therapies (infliximab). Prior colonoscopy revealed the presence of ~50 sessile reddish polyps, mainly located in the rectosigmoid area. Biopsy specimens of the polyps showed superficial erosion with elongated hyperplastic glands and a mixed inflammatory infiltrate in the lamina propria. There was no atypia or dysplasia. Biopsy specimens of the intervening mucosa were not available. Laboratory values, including complete blood count, electrolytes, and serum protein, were within normal limits. Stool culture, ova and parasite examination and PCR for *Clostridium difficile* toxin B and cytomegalovirus were all negative. Despite the intake of infliximab, abdominal symptoms persisted, and the patient underwent a total proctocolectomy with anal preservation and end-ileostomy.

On gross examination, the proctocolectomy specimen contained numerous sessile reddish polyps measuring up to 30 mm in diameter (Figure 1A). These polyps were all on the apices of transverse mucosal folds (Figure 1B). A 20-mm cystic intramural lesion was identified in the rectum (Figure 1C,D). Further examination revealed no signs of diverticulosis. Histologically, the surface of the polyps was ulcerated and covered by a cap of fibrinopurulent exudate (Figure 2A). Polyps were composed of elongated crypts, without dysplasia. The lamina propria contained a mixed inflammatory cell infiltrate and smooth muscle bundles arranged perpendicularly to the muscularis mucosae (Figure 2B). The cystic structure corresponded to a localized form of colitis cystica profunda (CCP)-type lesion, being located in the submucosa (Figure 2C). Its wall was lined by partially denuded, benign mucinous epithelium, and contained some calcifications (Figure 2D). The mucosa between the polypoid lesions was normal, which excluded the diagnosis of ulcerative colitis made preoperatively. The loop ileostomy was closed 3 months after proctocolectomy.

Cap polyposis is a poorly recognized condition with distinct clinical, colonoscopic and pathological features. This entity is characterized by multiple inflammatory colonic polyps covered by a cap of granulation tissue; hence the name 'cap polyposis'.³ Its