The evolving spectrum of endocervical adenocarcinoma in situ (AIS)

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The incidence of endocervical adenocarcinoma (ECA) has increased recently. Most ECAs are causally related to persistent infection with oncogenic high-risk human papillomavirus (HPV) (HPV-associated) while about 20% are HPV-independent. The current 2014 World Health Organization (WHO) Classification classifies ECA largely on the basis of poorly reproducible morphological features and does not reflect the clinically relevant HPV-associated and HPV-independent pathways, the latter typically presenting at higher stage and having a worse prognosis [1]. Recently, a new International Endocervical Adenocarcinoma Criteria and Classification (IECC) scheme has been proposed which divides ECA into HPV-associated and HPV-independent types [2]. The new WHO Classification to be published in 2020 will also classify ECA as HPV-associated and HPV-independent.

With regard to precursor lesions of ECA, the current WHO Classification includes a single category of adenocarcinoma in situ (AIS) with no division into HPV-associated and HPV-independent types [1]. The precursor lesions of HPV-associated ECA are well known and comprise usual-type (endocervical-type) AIS and the much more uncommon stratified mucin-producing intraepithelial lesion (SMILE) which is considered in WHO 2014 to be a variant of AIS but which has also been suggested by one of us (WGM) to be best regarded as a form of high-grade reserve cell dysplasia [3]; both are associated with high-risk HPV, most commonly types 16, 18, and 45. Intestinal differentiation in the form of goblet cells can occur. Immunohistochemically, p16 exhibits block-type positivity (diffuse strong nuclear and cytoplasmic staining of virtually every cell). These lesions develop at the

transformation zone in patients with an approximate mean age of 40 years.

Our understanding and appreciation of the existence of HPV-independent precursor lesions of ECA has evolved only recently and this will also be reflected in the upcoming WHO Classification where AIS will be divided into HPV-associated and HPV-independent types. A welcome addition to the limited literature on HPV-independent AIS is a study by Asaka et al. which appears in this issue of Virchows [4]. We briefly review the current knowledge regarding HPV-independent AIS followed by a discussion of the strengths and weaknesses of the aforementioned paper and finally, we discuss our approach to these lesions and suggest areas where future study is needed.

Currently, it is thought that gastric-type adenocarcinoma, which encompasses the morphologically well-differentiated adenoma malignum, and which is the most frequent HPV-independent cervical adenocarcinoma develops from a related spectrum of rare benign and premalignant lesions exhibiting gastric differentiation. The benign lesions are represented by simple and complex gastric (pyloric) metaplasia, type A tunnel clusters and lobular endocervical glandular hyperplasia (LEGH), and the premalignant lesions by atypical LEGH and gastric-type AIS (G-AIS) [5–9]. The spectrum of benign, premalignant, and malignant gastric-type lesions may occur in patients with Peutz Jeghers syndrome. The direct precursor lesions of gastric-type adenocarcinoma are considered to be atypical LEGH and G-AIS. Intestinal differentiation in the form of goblet cells can occur in LEGH, atypical LEGH, and G-AIS. It has been suggested that G-AIS and atypical LEGH be lumped together until the generic term G-AIS because they are both considered to be precursors of gastric-type adenocarcinoma [9]. p16 is negative or exhibits patchy non-block-type immunoreactivity in these lesions.

The study by Asaka et al. included 36 cases of AIS and 25 cases of LEGH and classified cases of AIS based on their immunophenotype using a panel of cell lineage-specific markers comprising claudin 18 (CLDN18) (gastric epithelial marker), cadherin 17 (CDH17) (intestinal epithelial marker), and PAX8 (Müllerian epithelial marker), in association with

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HPV testing [4]. The cases of AIS were immunophenotypically classified as G-AIS, intestinal-type (I-AIS), gastrointestinal-type (GI-AIS), Müllerian-type (M-AIS), and AIS, not otherwise specified. All 25 LEGHs were categorized as gastric-type. All cases of LEGH and G-AIS were diffusely positive for CLDN18; expression of this marker was observed in 40% of I-AIS. CDH17 expression was observed in all I-AIS. In GI-AIS, both CLDN18 and CDH17 were diffusely positive. PAX8 expression was present in all “Müllerian type” AIS. All G-AIS were HPV-negative while most I-AIS and GI-AIS were HPV-positive [4]. Strengths of this study include the relatively large number of cases of HPV-independent AIS which are rare lesions making their study problematic, the fact that there has been minimal description of such lesions in the literature, and the use of cell lineage-specific markers. However, we disagree with the authors in their terminology. Since essentially all of these precursor lesions are of Müllerian origin, we prefer the term HPV-associated to M-AIS. Moreover, we disagree with including separate categories of G-AIS, I-AIS, and GI-AIS; we feel this is an overcomplication and our approach to this is detailed in the next paragraph.

As mentioned above, intestinal differentiation in the form of variable numbers of goblet cells may occur in both HPV-associated and HPV-independent AIS. As such, the term I-AIS has been used in the literature to denote both HPV-associated and HPV-independent variants of AIS (as in invasive adenocarcinomas). For this reason, we discourage the use of the term I-AIS and suggest that HPV-associated examples (block-type p16 immunoreactivity and high-risk HPV ISH positive) be termed usual HPV-associated type with intestinal differentiation and HPV-independent variants (p16 negative or non-block-type and negative HPV ISH) be termed G-AIS. While the term GI-AIS would be more appropriate than gastric-type given the potential for intestinal differentiation, the “gastric” terminology is well established in the literature for both in situ and invasive lesions. Interestingly, a prior study suggested two types of I-AIS: an HPV-associated type occurring in younger women and an HPV-independent type in older women [10].

As discussed, the upcoming 2020 WHO Classification will divide precursor lesions of ECA into HPV-associated and HPV-independent. Much is known about HPV-associated AIS but there is little information regarding HPV-independent precursors. Future studies of larger numbers of these lesions are required to document their full morphological spectrum, immunophenotype, molecular features, risk of neoplastic transformation, and optimal management. Given the rarity of these lesions, this will likely only be achievable through collaborative studies. Future studies should also aim to elucidate the precursor lesions of other HPV-independent

adenocarcinomas (mesonephric, clear cell, and endometrioid) which are even more uncommon than gastric-type.

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