Non-human papillomavirus virus-related cervical neoplasms

Andres A Roma

Oluwole Fadare

Abstract

Cervical cancer is a heterogeneous disease composed of mainly squamous and glandular lesions. The majority of the squamous lesions as well as glandular (endocervical) carcinomas are HPV-associated. Small but growing subgroups of adenocarcinoma are non-HPV related; this includes adenocarcinoma subtypes with uncertain association and a new subtype of adenocarcinoma recently introduced in the 2014 World Health Organization Classification of Tumours of Female Reproductive Organs named gastric type adenocarcinoma, included as part of the mucinous carcinomas.

In this review we will describe each of the subtypes of endocervical adenocarcinomas, its association or not with HPV and a more detailed description of those non-HPV related.

Keywords cervical cancer; endocervical adenocarcinoma; gastric-type adenocarcinoma; human papillomavirus virus; usual type endocervical adenocarcinoma

Introduction

Uterine cervix cancer is the third most common gynecological cancer after uterine corpus and ovarian cancers, and is also the third leading cause of cancer death among gynecological malignancies.[1] Cervical cancers primarily arise at the transformation zone located where the squamous epithelium of the ectocervix transitions to the glandular epithelium of the endocervical canal. Most these tumors are associated with persistent high-risk Human Papillomavirus Virus (HPV) infection and correspond to epithelial squamous and endocervical (glandular) carcinomas.[2–6] However, there is a small subset, in particular morphologic subtypes of adenocarcinoma that have not been associated to high-risk HPV.

The 2014 World Health Organization Classification of Tumours of Female Reproductive Organs classifies endocervical adenocarcinoma into several histologic subtypes.[2] The most common subtype, constituting 90% of all cases, is the usual type (formerly known as mucinous carcinoma, endocervical type or endocervical type adenocarcinoma, not otherwise specified). Studies have shown that high-risk HPVs are present in over 90% of usual type endocervical carcinoma, and nearly all cases of adenocarcinoma in-situ. In contrast, many of the other subtypes are either thought to be either HPV independent or have an association with high-risk HPV that has not been well-established. In this review, we will summarize key features of these HPV-independent carcinomas as well as related lesions.

Andres A Roma *MD Department of Pathology, University of California, San Diego, CA, USA. Conflicts of interest: none.*

Oluwole Fadare *MD Department of Pathology, University of California, San Diego, CA, USA. Conflicts of interest: none.*

Mucinous carcinoma

The mucinous carcinoma group is composed of different subtypes of endocervical carcinoma with some degree of mucinous differentiation (Figure 1 A–D).

Mucinous carcinoma, gastric-type

These tumors encompass a spectrum of adenocarcinomas with gastric or pyloric gland phenotype, highlighted by immunoreactivity for HIK1083 and/or MUC6.[7–9] According to Japanese studies, these tumors may represent 25% of the cervical adenocarcinomas.[7] Mean age at presentation was reported at 50 years (range 30–66 years) while endocervical adenocarcinomas, usual type, presented at least a decade earlier in average.[9]

Morphologically, the hallmark of this tumor is the presence of cells showing abundant or voluminous, pale or eosinophilic cytoplasm with prominent or distinct cell borders. Most tumors have prominent cytologic atypia. However, when these tumors are well differentiated, they have been diagnosed as minimal deviation adenocarcinomas, also known as "adenoma malignum of the uterine cervix".[4]

Adenoma malignum is a neoplasm that was described in the 19th Century, and is characterized by its deceptively bland histologic features.[10,11] It is usually a very challenging diagnosis and in occasion, multiple biopsies may be required before a definitive diagnosis can be rendered. However, in resections, these tumors are either deeply invasive and/or show areas with more definitively atypical features, which facilitates their recognition as malignant. Microscopic features that are most helpful in establishing the diagnosis of adenoma malignum include the presence of markedly irregular, abnormally shaped glands, invasion of the cervical wall, a loose edematous or desmoplastic stromal response and vascular or perineural invasion.[10,11] In a study by Gilks and collaborators, more than half the patients died of disease, several were alive but with recurrence and only three patients were alive with no disease after 2 years of follow-up.[11] Today, these tumors are considered an extremely well-differentiated variant of gastric-type adenocarcinoma.

Another lesion that is thought to exist in the spectrum of gastric-type lesions, is lobular endocervical glandular hyperplasia (LEGH), alternatively termed intestinal and pyloric glandular metaplasia by other investigators.[12–15] In a seminal report, Nucci and collaborators described a proliferation of "small to moderately sized rounded glands surrounding a larger centrally located gland" in a lobular configuration. The lobular proliferation was confined to the inner half of the cervical wall; the glands were lined by columnar mucinous cells similar to the normal endocervix but lacked expression with carcinoembryonic antigen.[12] Reactive atypia and mitoses were reportedly present, but the cells lacked significant cytologic atypia. Additional pertinent negative findings included lack of irregular stromal infiltration or desmoplastic stromal response. After a mean follow-up of 3.4

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Roma AA, Fadare O, Non-human papillomavirus virus-related cervical neoplasms, Diagnostic Histopathology (2017), https://doi.org/10.1016/j.mpdhp.2017.11.011

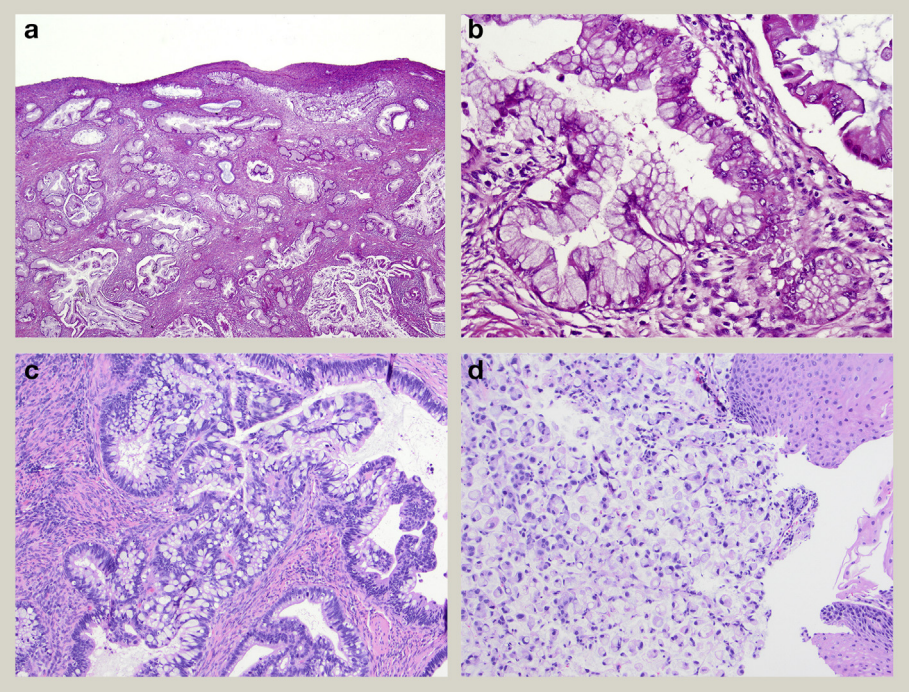

Figure 1 (**a**) Diffuse proliferation of bland appearing mucinous glands with haphazard arrangement and inconspicuous nuclei consistent with minimal deviation adenocarcinoma (adenoma malignum). H&E 40×. (**b**) High grade examination of mucinous proliferation composed of cells showing abundant or voluminous pale cytoplasm with prominent or distinct cell borders and nuclei with prominent cytologic atypia. H&E 200×. (**c**) Endocervical adenocarcinoma with cells showing prominent mucin content resembling intestinal goblet cells. H&E 100×. (**d**) Mucinous carcinoma with prominent signet-ring cells underlying squamous mucosa. H&E 100×.

years, all patients were alive with no recurrence of the lesion. The authors considered the lesion a pseudoneoplastic process.[12]

Around the same time, investigators in Japan described a similar lesion which they termed pyloric glandular metaplasia (PGM).[4,13] They noted that this lesion was characterized by pale eosinophilic cytoplasm of the columnar cells filled with predominantly periodic acid-Schiff (PAS) positive neutral mucin resembling gastric pyloric glands while normal endocervical glands were characterized by pale or bluish basophilic cytoplasm composed of alcian blue-positive mixed type mucins.

Although LEGH was initially considered to be pseudoneoplastic, several reports of the lesion with focal cytologic atypia, and/or association with minimal deviation adenocarcinomas and mucinous adenocarcinomas with higher degree of atypia (likely gastric-type adenocarcinoma) raised the possibility that LEGH is a precursor lesion.[14] Molecular and clonality studies revealed common alterations between these lesions, including recurrent chromosomal imbalances, such as gains of chromosome 3q and loss of 1p in 21% of LEGH. DNA samples of LEGH were extracted from somewhat atypical glandular epithelium by using microdissection technique, implying that LEGH with cellular atypia possess chromosomal imbalances related to minimal deviation adenocarcinomas.[14,15] These lesions were negative for HPV DNA.

Recently, Talia and collaborators reported a new entity termed gastric-type adenocarcinoma in-situ.[16] The authors theorize that it "represents a precursor to gastric-type adenocarcinoma of the cervix" and that this lesion and atypical LEGH are "related entities within a spectrum of premalignant gastric-type lesions for which they propose the umbrella term gastric-type adenocarcinoma in-situ".[16]

Since these tumors do not have association with HPV, they lack diffuse expression of p16, a helpful feature to differentiate them from endocervical adenocarcinoma of the usual type, which classically expresses p16 diffusely.[7,9] As was previously mentioned, additional immunostains that highlight these tumors include MUC6 and HIK1083; studies have shown that CK7, CEA, carbonic anhydrase IX, PAX8, CA19.9, CA-125, and hepatocyte nuclear factor 1 beta are also positive, p53, CDX2, and CK20 display variable expression, while estrogen receptors, progesterone receptor, PAX2, HER2/neu, and vimentin are negative.

Regarding prognosis, gastric-type adenocarcinomas behave as aggressive tumors with significantly worse disease specific survival than endocervical adenocarcinoma, usual type; gastric-type adenocarcinoma specific survival ranges from 30 to 42% at 5 years.[7,9] Between 43 and 59% of patients present with advanced stage disease (FIGO II–IV) and are more likely to have extracervical infiltration.[7,9] Patients appear to show ovarian involvement (35%), abdominal disease (20%) and 12% experienced extraperitoneal recurrences, more commonly than patients with endocervical adenocarcinoma, usual type.[9]

Since early detection of squamous carcinomas have reduced their incidence and HPV vaccination programs are projected to decrease HPV-associated lesions, gastric-type adenocarcinoma has the potential to increase in incidence in the future, making its recognition paramount.

Mucinous carcinoma, intestinal type

These are very rare tumors that recapitulate the morphology of intestinal carcinomas, given that they variably display goblet cells, argentaffin and Paneth cells.[2] Studies vary in the

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Roma AA, Fadare O, Non-human papillomavirus virus-related cervical neoplasms, Diagnostic Histopathology (2017), https://doi.org/10.1016/j.mpdhp.2017.11.011

Download English Version:

https://daneshyari.com/en/article/8807328

Download Persian Version:

https://daneshyari.com/article/8807328

Daneshyari.com