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Commentary

Controlling Human Papilloma Virus: A Public Health Perspective of Treatment of Anogenital Warts

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Disclosures of potential conflicts of interest may be found at the end of this article.

Human Papilloma Virus (HPV) infection is a global problem, and concerted efforts by gynecologists around the world for screening women for HPV have significantly reduced the incidence of HPV-related cancers of the female genital tract [1]. The success of HPV screening is largely due to clear-cut guidelines on detection and management of premalignant HPV lesions. The 2012 guidelines for cervical cancer screening are joint recommendations of the American Society for Clinical Pathology, the American Society for Colposcopy and Cervical Pathology, and the American Cancer Society, and were later also accepted by the American Congress of Obstetricians and Gynecologists [2]. In short, pathologists and gynecologists have extensively collaborated on this topic to reach broad consensus on who should be tested and how to manage premalignant HPV lesions. The introduction of HPV vaccines has further helped in the fight against HPV. While the gynecologists screen asymptomatic patients with no visible lesions, the urologists and dermatologists treat visible and often disfiguring anogenital warts with destructive methods and without bothering to get genotyping or a histopathological examination done. There is an elaborate algorithm to approach a case of low-grade squamous intraepithelial lesion (LSIL), which are presumed to be caused by low-risk HPVs [3]. The management of LSIL includes colposcopy or retesting depending on whether HPV testing was initially performed or not [3]. The rationale for colposcopy in a case of LSIL is to rule out a coexistent high-grade squamous intraepithelial lesion. If a high-grade squamous intraepithelial lesion is detected, management is done according to appropriate protocol. A meta-analysis reported cervical intraepithelial neoplasia (CIN)-II rates of 17% and CIN-III rates of 12% in colposcopic biopsies done for LSIL [4].

However, when the same low-risk HPV causes a visible anogenital wart, it is considered innocuous and not subjected to histopathology or genotyping. It is difficult to explain this difference in the approach for the same virus.

The reason for this difference in approach is the presumption that all anogenital warts harbor only low-risk HPVs. However, it is common knowledge that dysplasia in anogenital warts does occur [5]. Coinfection of both low- and high-risk HPV in the same lesion has also been documented [6]. The role of HPV testing in cervical screening is firmly established. Combined HPV and cervical smear screening (also called HPV cotesting) and the role of primary HPV testing as the sole modality of screening are being investigated [7]. HPV cotesting can increase the interval period for cervical screening to 5 years under the current guidelines. Similar studies on HPV genotyping of anogenital warts have shown that a significant proportion of these lesions harbor high-risk HPV in combination with low-risk HPV [8]. While it is true that the majority of these infections would heal themselves within 2 years and cause no sequalae, a small number would persist and potentially cause cancers of the cervix, oropharynx, and oral cavity.

Extragenital HPV is very common in patients with anogenital warts and has been documented in oral rinse samples as well [9]. Patients with anogenital warts have also been shown to have a higher risk of anogenital and head and neck cancers [10]. Recent reviews have also shown an increase in cases of HPV-related oropharyngeal cancers amongst patients with limited exposure to tobacco and alcohol [11]. If the increasing trend continues, then the annual number of HPV-related cancers of oropharynx would surpass the number of HPV-related cervical cancers by 2020 [12].

Another cancer whose incidence has increased in the past decade is HPV-related anal cancer, particularly amongst men who have sex with men and HIV patients. According to an estimate, about 88% of all anal cancers worldwide are associated with HPV [13]. Anal cytology and HPV genotyping have been used extensively to diagnose preinvasive HPV lesions in this setting, taking a cue from the enormous success of Pap smear in reducing cervical cancer [13].

Despite such compelling evidence that anogenital warts are not as innocuous as they seem to be, there has been no change in our management strategies. The main reason is that most of the doctors think about prevention of cancers pertaining to their own specialties. The fight against cervical or head and neck cancers is not the responsibility of gynecologists or ear, nose, and throat surgeons alone. The dermatologists, urologists, and general surgeons are all equally important players and should contribute. The other weapon is patient education. Patients need to be made aware that anogenital warts have an association with anogenital cancer, as well as head and neck cancer.

Whenever destructive methods of treatment for anogenital warts are used, at least a part of the lesion should be submitted for genotyping or histopathology. If high-grade dysplasia is

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noted on histopathology and genotyping is not available, then p16 immunohistochemistry can be used as a surrogate marker for high-risk HPV infection [5, 6]. If high-risk HPV is detected, then appropriate partner screening should be done for all sexual contacts of the patient.

In a similar way, vaccination efforts have largely focused on the female population. Similar thrust needs to be given to vaccination of males [14]. By ignoring half of the population, we are never going to win the war against HPV. Only when a large proportion of the population is vaccinated against HPV will we be able to achieve herd immunity against the virus. We have effective vaccines against both low- and high-risk viruses. Vaccinating the population on a large scale makes sense in terms of savings on the treatment of HPV-related malignancies and also the cost of treating anogenital warts.

The introduction of quadrivalent and nine valent vaccines that protect from low-risk (HPV-6, 11) and high-risk HPV (notably HPV-16, 18) is a step in the right direction. HPV-related anogenital diseases, which include anogenital warts, cervical carcinomas, and anal carcinomas, need to be addressed as one entity [15].

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