



CERVICAL CANCER IN WOMEN LIVING WITH HIV: A REVIEW OF THE LITERATURE

F. D'ANDREA¹, G. F. PELLICANÒ², E. VENANZI RULLO^{1,3}, F. D'ALEO¹, A. FACCIOLÀ¹,
C. MICALI¹, M. COCO¹, G. VISALLI⁴, I. PICERNO⁴, F. CONDORELLI⁵, M. R. PINZONE^{3,6},
B. CACOPARDO⁶, G. NUNNARI¹, M. CECCARELLI^{1,3}

¹Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

²Department of Human Pathology of the Adult and the Developmental Age "G. Barresi", University of Messina, Messina, Italy

³Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

⁴Department of Biomedical and Dental Sciences and Morpho Functional Imaging, University of Messina, Messina, Italy

⁵Department of Pharmacological Sciences, Università del Piemonte Orientale "A. Avogadro", Novara, Italy

⁶Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Catania, Italy

Flavia D'Andrea and Giovanni Francesco Pellicanò equally contributed to this work

Abstract: *The introduction of ART had a significant impact on PWLH survival. The incidence of AIDS-defining cancers has decreased, but the risk is still higher than general population. Women living with HIV have a high prevalence of HPV infection and related disease, including cervical cancer. HIV-related risk factors, such as immunodeficiency and chronic persistence of infection play an important role in its pathogenesis. HPV vaccine, screening and early antiretroviral therapies, are recommended to reduce the risk of developing cervical cancer. In this review, we considered the studies published about cervical cancer in PLWHA that we found performing a research on PUBMED (Bethesda MD, USA) with the following research terms "Papillomavirus", "Cervical Cancer", "HIV infection", "Screening", "Vaccination" with the aim to point out the main aspects of cervical cancer in HIV infected women, its management and prophylaxis.*

KEYWORDS: *Cervical cancer, Human immunodeficiency virus (HIV), Human papilloma virus (HPV), Screening, Vaccination.*

INTRODUCTION

Cervical cancer is one of the most common cancers worldwide: with about 500,000 new cases and 270,000 deaths, it represents an important cause of morbidity and mortality in women around the world¹. However, because of healthcare disparities, high incidence and mortality rates are predominant in developing countries where screening programs are limited or absent². The most important risk fac-

tor for cervical cancer development is persistent HPV infection. Most sexually active women will be infected by HPV during their lifetime but for many women the infection is cleared by the immune system. However, some women can develop persistent HPV infections, which might progress into low or high-grade cervical intraepithelial neoplasia (CIN) and invasive carcinoma. As for many other cancers and diseases, people living with HIV (PLWH) have a higher risk to develop cervical cancer³⁻²⁴. HPV



infection occurs more frequently in women living with HIV than the general population: the incidence has significantly decreased after the introduction of the Highly Active Antiretroviral Therapy (HAART) but the risk of chronic infection and progression to high-grade intraepithelial lesions and cervical cancer is still higher among HIV-infected women²⁵. Immunosuppression plays an important role on the natural history of HPV infection allowing its persistence: the risk of developing cancerous and pre-cancerous lesions is inversely proportional to CD4⁺ T-lymphocyte counts²⁶. Several studies showed a predominance of advanced disease at the time of diagnosis compared to general population and a poorer treatment outcome²³. Furthermore, the progression from a high-grade lesion to cancer is faster in WLHA than in the general population²⁷. Peculiar features of HIV-related cervical disease are the high frequency of extensive lesions, multifocality and the high percentage of relapses²⁸. Moreover, clinical manifestations of invasive cancer often occur at a younger age than uninfected women²⁹.

In this paper, we reviewed the literature available about cervical cancer, to highlight the keypoints of current diagnosis, management and prophylaxis.

MATERIALS AND METHODS

On October 15th, 2018, we performed a review of the literature to identify the link existing between Cervical Cancer, Human Papilloma Virus (HPV) infection and Human Immunodeficiency Virus (HIV) infection. We searched PubMed applying “(“Cervical Cancer”, “Papillomavirus”, “HIV infection”, “Screening”, “Vaccination”)”. We included only recent articles written in English, identifying 57 records. We excluded 9 articles after reading title and abstract. At the end of the assessment we included in our review the 48 full-text articles.

ETIOLOGY

Human Papilloma Virus (HPV) is a small, non-enveloped deoxyribonucleic acid (DNA) virus with a marked tropism for epithelial cells of skin or mucosal membrane, causing lesions anywhere on the cutaneous and mucosal surface. Its capsid is composed of 72 capsomers, which contain at least two capsid proteins, L1 and L2. The HPV genome consists of a single molecule of double-stranded, circular DNA³⁰. The genome is divided into three regions: the first one is a non-coding regulatory region. It contains the p97 core promoter with enhancer and silencer sequences. They regulate DNA replication by controlling the transcription of the ORFs. The second is

an early region, consisting of ORFs E1, E2, E4, E5, E6, and E7, involved in viral replication and oncogenesis. The third is a late region, which encodes the L1 and L2 structural proteins for the viral capsid. There are over 80 different HPV subtypes, divided into high-risk HPV (subtypes -16; 18; 31; 33; 35) most frequently associated with a persistent infection leading to invasive cancer, and low-risk HPV (subtypes 6, 11, 40, 42, 43)¹⁹. HPV-16 and HPV-18 are responsible for most of the neoplastic lesions; they also cause other neoplasms, including vaginal, anal and oropharyngeal cancers¹⁹.

RISK FACTORS AND PATHOGENESIS

Persistence of high-risk HPV infection is necessary for the development of cervical cancer and it represents the most important known risk factor³¹. Other risk factors are: sexual behavior, the use of combined oral contraceptives, multiparity, smoking and immunosuppression³².

HIV-induced immune deficiency increases the risk of cancer with a permissive mechanism, promoting the accumulation of genetic damage and progression from dysplasia to cancer²⁵.

HPV-DNA is found integrated into the host's genome in many HPV-associated cancers³³.

HPV-16 and -18 encode for three oncoproteins (E5; E6; and E7): these oncoproteins stimulate growth and have transforming properties. The integration of HPV-DNA within the host genome results in chromosomal instability and favors the progression from CIN to invasive carcinoma. Immunosuppression caused by HIV infection prevents the clearance of HPV, leading to a gradual loss of control over HPV replication³⁴.

SYMPTOMS

Invasive carcinoma is asymptomatic in an early stage. When tumor deeply invades the tissues, the most common symptom is occasional blood loss, often post-coital, unrelated to the menstrual cycle.

Another frequent symptom is leucorrhoea. Unilateral pelvic pain, anemia, lower limbs edema, vaginal bleeding, loss of urine and / or feces from the vagina are signs and symptoms of advanced disease³⁵.

PRIMARY PROPHYLAXIS AND SCREENING

HPV is detected in almost all cases of cervical cancer and in the majority of vulvar, head and neck, vaginal, and anal cancers¹⁹.

Cervical cancer is preventable through anti-HPV vaccination and appropriate screening programs²¹.

Prophylaxis is based on vaccination: vaccination against high-risk HPV subtypes is recommended for females and males starting at age 11 or 12 years³⁶.

Three anti-HPV vaccines based on virus-like particles of the L1 capsid protein are available: Cervarix™ (GlaxoSmithKline), the bi-valent vaccine against HPV-serotypes 16 and 18, the quadrivalent Gardasil (Merck & Co., Inc., Kenilworth, NJ, USA), against HPV-serotypes 6, 11, 16 and 18 and the nine-valent Gardasil-9 (Merck & Co., Inc., Kenilworth, NJ, USA), against HPV-serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58. Several data from HIV negative population have confirmed vaccine safety and efficacy^{37,38}.

Among HIV-negative women, in fact, the quadrivalent HPV vaccine demonstrated 98% efficacy for preventing CIN and 100% of genital warts, and similar results were also reported with 9-valent HPV vaccine³⁹.

Kojic et al⁴⁰ examined safety and serostatus of HPV types 6, 11, 16, and 18 in HIV-infected women. They showed that the quadrivalent HPV vaccine is safe and immunogenic among women aged 13-45 years who were seronegative, with a percentage of seroconversion >75% for all 4 HPV types included in the vaccine. In HPV-seropositive women, vaccination induced a significant increase in antibody levels. Moreover, seroconversion proportions were higher among women with baseline CD4 cell counts >200 cells/ μ L.

HPV vaccination can potentially prevent cervical cancer: this is the reason why HPV vaccination must be recommended not only for young girls, but also for boys and HIV-infected people¹⁹.

It is important ensuring an appropriate antibody response to HPV vaccine to establish long-term immunity. WLWH have a high risk of developing precancerous lesions and invasive carcinomas, but a timely screening allows early detection and treatment, leading to a significant reduction in mortality²¹. Screenings are systematic examinations aimed at identifying the pathology at an early stage, allowing better possibilities of treatment and prognosis. A screening test must satisfy some criteria: it must be safe, without side effects; moreover, it should be well tolerated by the patient and sustainable from an economic point of view. There are now three major alternatives for cervical cancer screening: cytology, HPV testing, and cytology-HPV co-testing. Cytology-based screening is still the most frequent one: it is a cervical cytological examination that can be performed with conventional smear or with liquid preparation systems. If any abnormality is detected by Pap-Test, colposcopy is needed. Cervical cancer screening for general population is recommended

every 3 years for women aged 25 to 64. According to the new 2017 Guidelines, screening for HIV + women must start at the diagnosis: the second test should be repeated at 12 months; if 3 annual Pap smears are negative, it should be repeated every 3 years⁴¹. New recommendations support HPV testing strategies: in fact, hr-HPV infection is needed for developing cancer and hr-HPV DNA is present in the context of lesions. For these reasons molecular test is a good approach to identify women with high-grade CIN⁴². Co-testing is currently recommended as the best screening option in the US, while it is not in Europe or Australia⁴³.

MANAGEMENT AND THERAPY

Management of cervical cancer provides adherence to ART, monitoring drugs interaction during cancer therapy and psychological support of the women^{19,44}. Staging of cervical cancer consists in a combination of pelvic exam, chest x-ray and abdominal ultrasound to exclude metastasis⁴⁵.

The interactions between ART, HPV and cervical lesions in HIV infected women are poorly understood and the effect of ART on the lesions is not well established⁴⁶.

Several studies have shown that effective therapy was associated with a reduction in high-risk HPV persistence⁴⁵. Furthermore, we must consider that HIV-positive women live longer, and they are more subjected to the DNA and somatic damages caused by HPV chronic exposure. Treatment of Cervical Cancer include surgery, radiotherapy and chemotherapy⁴⁷.

Surgery plays an important role in the management of early stage cervical cancer: radical hysterectomy and lymphadenectomy are often needed.

Treatment of locally advanced cervical cancer includes RT (external RT and brachytherapy) and chemotherapy⁴⁶. In PLWH the prolonged CD4+ T-cell suppression induced by chemotherapy could negatively influence the course of HIV disease⁴⁸.

Quality of life of cervical cancer survivors can be influenced by late effects such as bladder and bowel dysfunction, sexual dysfunction, lymphedema and psychosocial problems⁴⁴. Surgical treatment and radiation therapy can lead to long-term sequelae such as atonic bladder, hydroureteronephrosis, incontinence, dysuria, hematuria, hemorrhagic cystitis. Diarrhea, steatorrhea, tenesmus, fecal incontinence and rectal bleeding represent some of the other complications that can occur. Fatigue, anxiety and depression are the most frequent psychosocial problems. Fear of recurrence and the breakdown in perception of the body image negatively affect patient's life after surgery and RT. For all these rea-



sons, management of cervical cancer must include psychological support during and after treatment and evaluation of long-term sequelae, improving quality of life.

CONCLUSIONS

The natural history of HIV infection has been profoundly modified by the introduction of HAART, but HIV-infected women still have a higher risk of developing HPV-related diseases, including cervical cancer. Vaccination and screening programs are essential weapons to fight cancer burden. Further studies are needed to obtain data about interactions between HAART and HPV-related lesions. Lastly, psychological support for cervical cancer survivors and management of late effects (if they occur) are needed.

CONFLICT OF INTEREST:

The Authors declare that they have no conflict of interests.

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