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CASE REPORT
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Histopathology and Immunohistochemistry In Cases of Giant Perianal Condyloma Acuminata with Squamous Cell Carcinoma Transformation

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Abstract:

Giant Condyloma Acuminata (GCA) considered a histologically benign tumor that is locally aggressive but has the potential for destructive growth and a high recurrence rate. Unusual clinical presentations of GCA with rapid growth may indicate malignant transformation. Histopathological examination is necessary for the diagnosis of Condyloma Acuminata to observe cell changes and the level of invasiveness. The purpose of this case report is to discuss the importance of the histopathological approach and immunohistochemistry with P16 and P53 antibodies in patients with Giant Condyloma Acuminata (GCA) with suspected Squamous Cell Carcinoma (SCC) transformation. A case of 42-years-old male came to the clinic with a chief complaint of anal warts. On venereological examination, there were verrucous plaques, multiple, clear borders, irregular edges, measuring 7x4 cm with varying shapes and ulcers with an erythematous base, multiple, firm borders, irregular edges, varying shapes and sizes. Also, blood and mucopurulent discharge were obtained. The acetowhite test showed positive results. On histopathological examination, the results showed hyperkeratosis, koilocyte cells, and invasion of the stroma. The histopathological examination was consistent with condyloma acuminata with a focus of SCC transformation. The patient underwent an immunohistochemical examination with P53 and P16 antibodies, the results were positive for P53 in 40% of tumor cells while P16 was negative. Histopathological examination is essential for the diagnosis of GCA, while immunohistochemical analysis can be employed to identify specific strains or antigens of HPV, which may expedite the evolution and progression of tumors from benign to malignant states. It can be concluded that GCA requires regular histopathological and immunohistochemical screening and examination for early detection of malignancy.

Keywords: Giant condyloma acuminata; Squamous cell carcinoma; Immunohistochemistry

Introduction

Giant Condyloma Acuminata (GCA), also known as Buschke-Lowenstein Tumor (BLT), is a rare disease that affects the anogenital area. GCA is considered a histologically benign tumor that is locally aggressive but has the potential for destructive growth and a high recurrence rate. The cause of GCA is associated with low-risk human papillomavirus (HPV) infection, predominantly HPV types 6 and 11. Infections with low-risk HPV types are typically asymptomatic or benign, and the lesions spontaneously disappear after some time, usually within weeks or months.[1] Benign condylomas can then progress to dysplasia and undergo transformation into squamous cell carcinoma (SCC), primarily due to HPV types 16 and 18.[2]

The occurrence of Giant Condyloma Acuminata (GCA) typically happens in individuals around 40 years old. The estimated incidence is approximately 0.1% in the general population, with a male-to-female ratio of 2.7:1. Symptoms of GCA include the presence of a slowly growing mass resembling a cauliflower in the genital or anorectal area, with relatively slow infiltration into deeper tissues. The disease originates from long-standing condyloma acuminata (CA) and can grow to a diameter of more than 10 cm. Tumor growth is generally slow but may be rapid in individuals with Human Immunodeficiency Virus (HIV). Unusual clinical presentations of GCA with rapid growth may indicate malignant transformation.[1]

Histopathological examination is necessary for the diagnosis of Condyloma Acuminata (CA), while immunohistochemical testing can be used to determine specific strains or antigens of HPV. Histopathological examination is performed to observe cell changes and the level of invasiveness, especially in cases of high-risk HPV infection. Biopsy is indicated for cases of atypical lesions, lesions with a doubtful diagnosis, large lesions, lesions unresponsive to therapy, and in immunocompromised patients.[3,4]

In cases of CA and Squamous Cell Carcinoma (SCC), immunohistochemical examinations such as P16 and P53 can be conducted as they may indicate malignant evolution.[3,4] In this case report, a 42-year-old male patient diagnosed with Giant Perianal Condyloma Acuminata with Squamous Cell Carcinoma Transformation will be presented.

Case

A 42-year-old male presented to the Dermatology and Venereology Clinic complaining of a lump in the anus. The patient reported experiencing the anal lump for the past 4 months. Initially, it appeared as a small, rough-surfaced lump, resembling a pea, in the anal area. Over the subsequent 2 months, the lump increased in size and multiplied. As the size of the lumps increased, they fused to form a large lump. The lump was prone to bleeding and fragile, occasionally leaving blood stains and whitish-yellowish fluid on the underwear. The patient also complained of intermittent pain rated at 5/10 on the Visual Analog Scale (VAS). Pain exacerbated when the lump rubbed or was pulled during activities, while pain during bowel movements was denied. No complaints of decreased appetite, recurrent diarrhea, or weight loss were reported. Other complaints included a wound on the penis, red spots appearing throughout the body, and discharge from the genitalia was denied.

The patient had no history of transfusion, transplantation, cancer, or diabetes mellitus. The patient got married one month ago and reported having intercourse with his wife a week ago without using condoms. Homosexual intercourse was denied by the patient. The patient admitted to having sexual relations with two ex-girlfriends and a sex worker five years ago. The encounters were

heterosexual, with condom use for genital-genital contact. The patient's partner had no complaints of genital warts. No history of genital wounds or discharge was reported before. The HIV and syphilis status of the partner is unknown, as the partner has not been tested due to unwillingness to come for testing.

The patient works as a mechanic and frequently travels out of town, currently residing with his parents and wife. The wife works as an admin in an office. The patient completed high school and started smoking at the age of 25. The patient bathes and changes underwear twice a day. The patient frequently cleans the anal area with warm water and antiseptic fluid.

On physical examination, the patient appeared mildly unwell, with a weight of 75 kg. The patient was conscious and alert. Vital signs were within normal limits. Conjunctiva and sclera were normal. No enlargement of lymph nodes was found in the neck, axilla, or groin regions.

Dermatological examination of the perianal region revealed multiple verrucous plaques with well-defined borders, irregular edges, and varying sizes and shapes, measuring 7x4 cm. Ulcerations with erythematous bases were also observed, with multiple, well-defined, irregular-edged, and variably shaped ulcers. Blood was present, and mucopurulent discharge was noted. The acetowhite test yielded a positive result (Figure 1).

The patient also underwent several additional diagnostic tests (Figure 2), including a Gram stain on discharge that revealed the presence of abnormal Polymorphonuclear (PMN) count and cocci. The darkfield test did not detect *Treponema pallidum*. Laboratory test results, including Venereal Disease Research Laboratory (VDRL), *Treponema Pallidum* Haemagglutination Assay (TPHA), and rapid HIV antibody test, showed non-reactive results.

Figure 1 Clinical features of the patient. Multiple verrucous plaques, with well-defined borders, irregular edges, and varying sizes and shapes. Blood (+), mucopurulent discharge (+), acetowhite test (+).

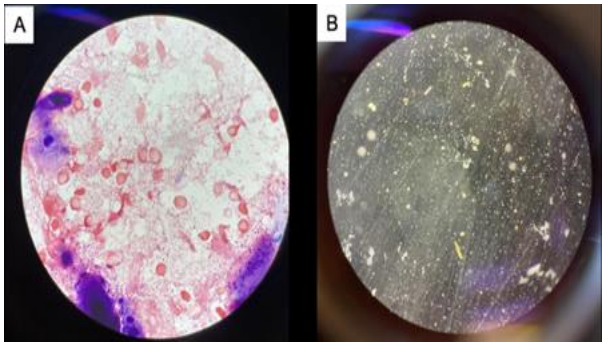

Figure 2 (A) Discharge sample at magnification → 1000x reveals polymorphonuclear leukocytes (PMN) and cocci on Gram Stain Examination. (B) On darkfield examination, there is no *Treponema pallidum* detected.

In the histopathological examination (Figure 3), sections of papillomatous tissue with complex squamous epithelial layers are observed, displaying partially acanthotic features, with some showing koilocytic characteristics. Visible invasive foci into the stroma are also noted, appearing atypical. In the sub-epithelial stroma, there is a dense accumulation of inflammatory cells, including neutrophils, lymphocytes, and histiocytes.

The biopsy result concludes condyloma acuminata with areas of Squamous Cell Carcinoma transformation.

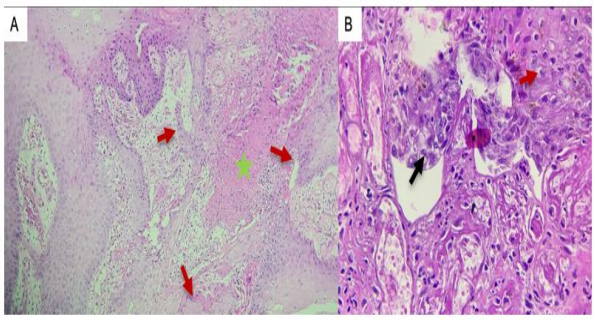

Figure 3 (A) There is a visible invasive focus, with areas of infiltration penetrate into the stroma (→), and necrotic tissue is observed (★) (H&E, 400x). (B) Atypical cells are evident, exhibiting a polygonal shape, increased nuclear-cytoplasmic ratio, and prominent nuclei (→). Koilocytic cells are also observed (→) (H&E, 1000x).

Subsequently, an immunohistochemical examination was performed using P16 and P53 antibodies (Figure 4). The P53 antibody test revealed positivity in approximately 40% of the tumor cell nuclei, while the P16 antibody test showed negativity in tumor cells. Thus, the immunophenotype supports the diagnosis of condyloma acuminata with a focus on Squamous Cell Carcinoma transformation.

Based on the anamnesis, physical examination, and supporting tests, the patient has been diagnosed with Giant Perianal Condyloma Acuminatum with Squamous Cell Carcinoma Transformation. The patient is referred to the oncology surgery department and diagnosed with condyloma acuminata in the anal region with suspected SCC transformation. The patient is scheduled for Abdominal and Inguinal Ultrasonography (USG) in October 2023. The patient is also educated about ABCDE for the prevention of STIs and advised to have their partner checked.

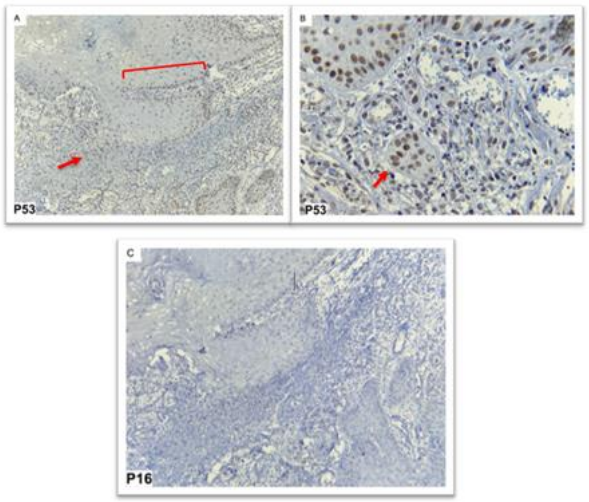

Figure 4 Immunohistochemistry. (A) P53 appears positive in approximately 40% of the tumor cell nuclei ([). Squamous cells are observed infiltrating the stroma (→) (400x). (B) Nesting in the stroma is evident, and there is proliferation of anaplastic squamous cells with enlarged nuclei (→) (1000x). (C) P16 appears negative in tumor cells (400x).

Discussion

Condyloma Acuminata (CA) is a benign tumor caused by human papillomavirus (HPV) infection, typically developing in the anogenital area. Approximately 90% of condylomas are caused by HPV types 6 and 11. Subsequently, KA can progress to dysplasia and undergo transformation into squamous cell carcinoma (SCC), especially after infection with HPV types 16 and 18.[2] In some literature, anal condyloma is described as "giant" when its size ranges from 5 cm to 30 cm, where Giant Condyloma Acuminata (GCA) is also known as Buschke-Löwenstein Tumor (BLT).[5] The occurrence of Giant Condyloma Acuminata (GCA) typically happens in individuals around 40 years old. The estimated incidence is approximately 0.1% in the general population, with a male-to-female ratio of 2.7:1 and it becomes more common

during pregnancy.[1] Risk factors for GCA include age, smoking habits, infection with HPV subtypes 6, 11, 16, and 18, immunosuppressive conditions such as HIV infection, the use of corticosteroids, immunomodulators, and diabetes mellitus, engaging in risky sexual behavior, coexistence with condyloma, and association with specific HLA genes.[6]

Human Immunodeficiency Virus (HIV) is an infectious ailment that selectively affects the human immune system through the assault on cluster of differentiation CD4 cells.[7] The prevalence of HIV/AIDS cases in Indonesia displays a consistent annual increase. According to the HIV/AIDS progress report provided by the Directorate General of Disease Control and Environmental Health at the Ministry of Health of the Republic of Indonesia as of March 2017, substantial numbers of individuals affected by HIV have been documented in major provinces of Indonesia. East Java, ranking second after DKI Jakarta, has reported a total of 33,043 cases. Notably, HIV infections exhibit an upward trend, particularly within the age groups of 25-49 years and 20-24 years, which are considered the productive age brackets.[8]

In certain conditions such as HIV infection, HPV 6 and 11 infections can progress unchecked, resulting in the development of GCA. Malignant transformation into squamous cell carcinoma may occur in over 50% of cases, with a higher incidence observed in individuals with HIV. The prevalence of CA in individuals with HIV infection ranges from 5% to 27%. Research indicates that 60% of men and 40% of women diagnosed with CA also have HIV. Men exhibit a higher risk behavior for acquiring CA in conjunction with HIV due to their increased sexual activity and a greater number of sexual partners compared to women[18].

HIV amplifies HPV transcription and upregulates HPV E7, leading to increased HPV DNA in infected tissues. The reduction in quantities of Langerhans cells, macrophages, and CD4 cells by HPV affects local immune control. This intricate interplay between HIV and HPV may elevate the risk of recurrence, even following surgical resection.[10]

In GCA, the most common location in males is the penis (81-94%), and in females, it is the vulva (90%). The second most common location for both genders is the perineum.[11] The clinical manifestations that arise include a slowly growing cauliflower-like mass in the genital or anorectal area. Anogenital warts can also be accompanied by symptoms such as pruritus, burning sensation, pain, and obstruction. Unusual clinical presentations of GCA with rapid growth indicate malignant transformation. Clinical symptoms that appear in patients leading to malignancy include infiltration or infection of surrounding soft tissues, easy bleeding, pain, the presence of lumps, itching in the perianal area, tenesmus, and changes in bowel habits.[4]

Giant Condyloma Acuminata (GCA) is diagnosed based on medical history, clinical presentation, and histological examination. Acetowhite testing involves examining HPV lesions using 3-5% acetic acid, where the lesions will turn whitish-gray due to the excessive expression of cytokeratin-10 (CK10) in the suprabasal cells infected with HPV. However, this test has low sensitivity and specificity.[12] Histopathological examination is required for the diagnosis of Condyloma Acuminata (CA), while immunohistochemical testing can be used to determine specific strains or antigens of HPV.[3] Histological examination can be performed to rule out the possibility of intraepithelial or invasive squamous cell carcinoma. All GCA cases should be biopsied due to the risk of malignant transformation.[13] In Condyloma Acuminata (CA), histological features include acanthosis, parakeratosis, papillomatosis, and koilocytosis, especially in the basal cell layer.

Koilocytes are cells with irregular nuclei, perinuclear circles, or perinuclear halos, and some may exhibit binucleation.[14] The histopathological characteristics of Squamous Cell Carcinoma (SCC) in the anal region involve mass infiltration with invasion into the stroma, prominent atypical nuclei, and the presence of necrotic tissue.[15]

Examinations can be conducted if there is suspicion of malignancy. In cases of Condyloma Acuminata (KA) and Squamous Cell Carcinoma (SCC), immunohistochemical examinations such as P16 and P53 can be performed. In immunohistochemistry, the examination of P16 is useful as a biomarker for high-risk HPV infection. P16 is also used as a biomarker in diagnosing high-grade cervical lesions, SCC, cervical cancer, and vulvar cancer. Cancers that overexpress P16 are generally caused by HPV.[3] Excessive expression of this P16 marker is interpreted as positive for high-risk HPV infection. Positive P16 examination results show full thickness or end block full thickness.[16] The TP53 gene encodes the tumor protein p53, also known as the genome guardian, which prevents genomic alterations and is classified as a tumor suppressor gene. The p53 gene is the most frequently mutated gene in cancer (>50%) and plays a crucial role in the development of neoplasms. Low levels of p53 indicate that the tumor has a low evolution rate towards malignancy, while high values suggest the presence of malignancy evolution.[3]

The treatment of GCA patients is often delayed. At the time of diagnosis, most patients present with large lesions showing malignant transformation. Early aggressive treatment is necessary to prevent the spread of GCA, extensive tissue damage, and the potential for malignant transformation. Due to the rarity of this disease, there are no specific guidelines for its treatment. A multidisciplinary approach involving surgeons, dermatologists, oncologists, pathologists, and radiologists is required.[17]

Conclusions

Giant Condyloma Acuminata (GCA) is a benign condyloma that can later progress to dysplasia and transform into Squamous Cell Carcinoma, primarily due to HPV types 16 and 18. Diagnosis and treatment of GCA with malignant transformation often occur late. At the time of diagnosis, most patients exhibit large lesions with malignant transformation.

For GCA patients, histopathological examination is necessary, followed by immunohistochemistry if atypical or invasive results are obtained. In the histopathology of GCA with SCC transformation, papillomatous tissue with complex squamous epithelial layers is observed, appearing acanthotic, with some showing koilocytic features. Suspicious invasive foci into the stroma are also evident, displaying atypical characteristics.

In immunohistochemistry, the examination of P53 and P16 is useful in detecting malignancy evolution in GCA. P53 is the most frequently mutated gene in cancer and plays a crucial role in neoplasm development. Low P53 levels indicate a low evolution rate to malignancy, while high values suggest malignancy evolution. P16 examination serves as a biomarker for high-risk HPV infection. Positive P16 results are found in high-risk HPV infections.

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