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Case Report

Unraveling the rarity: p16-positive and p53-positive locally advanced anal cancer in a person living with HIV

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Abstract

Introduction: Anal squamous cell carcinoma (ASCC) is rare in the general population but is associated with significant morbidity and mortality, particularly among people living with HIV (PLWH). Patient outcomes are influenced by human papillomavirus (HPV) status, immune function, and tumor biology.

Case Report: We report a case of a 56-year-old man with long-standing HIV infection on stable antiretroviral therapy (ART), diagnosed with locally advanced ASCC (T4N1cM0). He received standard concurrent chemoradiotherapy (CRT) with mitomycin C and 5-fluorouracil (5-FU). Treatment was complicated by Grade 3 febrile leukopenia, Grade 2 radiodermatitis, and scrotal lymphedema. An institutional COVID-19 outbreak caused an unplanned treatment interruption, extending the overall CRT duration to 70 days; the patient did not contract COVID-19. Therapy was resumed without dose modification. Six months post-treatment, imaging and endoscopic evaluation revealed fibrotic changes without evidence of active disease. At twelve months, however, the patient developed rapid locoregional recurrence and pulmonary metastases, with fistula and abscess formation, necessitating palliative care. Retrospective immunohistochemical analysis of the original tumor revealed strong p16 expression (indicative of transcriptionally active high-risk HPV), aberrant p53 expression, and a markedly elevated Ki-67 index (99%), reflecting aggressive tumor biology.

Conclusions: This case illustrates the challenges of managing ASCC in PLWH and underscores the need for optimized CRT protocols for this population. Reliable molecular biomarkers, including p16, p53, and Ki-67, may guide personalized therapy and improve prognostic stratification.

Key words: Anal squamous cell carcinoma; HIV; HPV; p16; p53; Ki-67; Case Report.

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Introduction

Anal cancer is an uncommon malignancy, accounting for approximately 2% of all gastrointestinal cancers, but it is associated with substantial morbidity and a non-negligible risk of disease-related mortality, particularly among high-risk groups. Human papillomavirus (HPV) infection and immunosuppression, especially in people living with HIV (PLWH), are well-established risk factors, with men who have sex with men (MSM) representing a particularly vulnerable population. These factors highlight the importance of targeted prevention strategies, early detection, and optimized treatment protocols [1].

Among anal malignancies, anal squamous cell carcinoma (ASCC) is the most prevalent histological subtype, and its incidence has been steadily increasing, particularly in immunocompromised populations [1,2]. Progression to ASCC is often preceded by precancerous lesions such as squamous intraepithelial lesions (SILs), also referred to as anal intraepithelial neoplasia (AIN). High-resolution anoscopy enables early detection of such lesions in high-risk individuals, facilitating timely intervention and structured surveillance programs, a method yet to be widely implemented in Serbia [2].

Clinical presentation of ASCC may include altered bowel habits, rectal bleeding, pain, discharge, and pruritus, although some patients remain asymptomatic [1]. These symptoms are frequently misattributed to benign anorectal conditions, such as hemorrhoids or fissures, resulting in delayed diagnosis and treatment initiation [1].

The standard first-line treatment for non-metastatic ASCC is definitive chemoradiotherapy (CRT), typically comprising external beam radiation therapy (total dose 54.0–59.4 Gy) combined with concurrent mitomycin C and 5-fluorouracil (5-FU). This approach yields an overall response rate approaching 80% in patients with stage T3–T4 and/or node-positive disease [3].

Given the central role of biomarkers in guiding

diagnosis and prognosis, growing attention has been directed toward p16, a surrogate marker of HPV-related oncogenesis, and p53, a tumor suppressor protein whose aberrant expression is often associated with treatment resistance and unfavorable outcomes. These markers are well-established prognostic indicators in head and neck cancers and are increasingly investigated in ASCC to better stratify patients and tailor therapeutic approaches [4,5]. However, their prognostic utility remains an evolving area of research, particularly in immunocompromised populations such as PLWH.

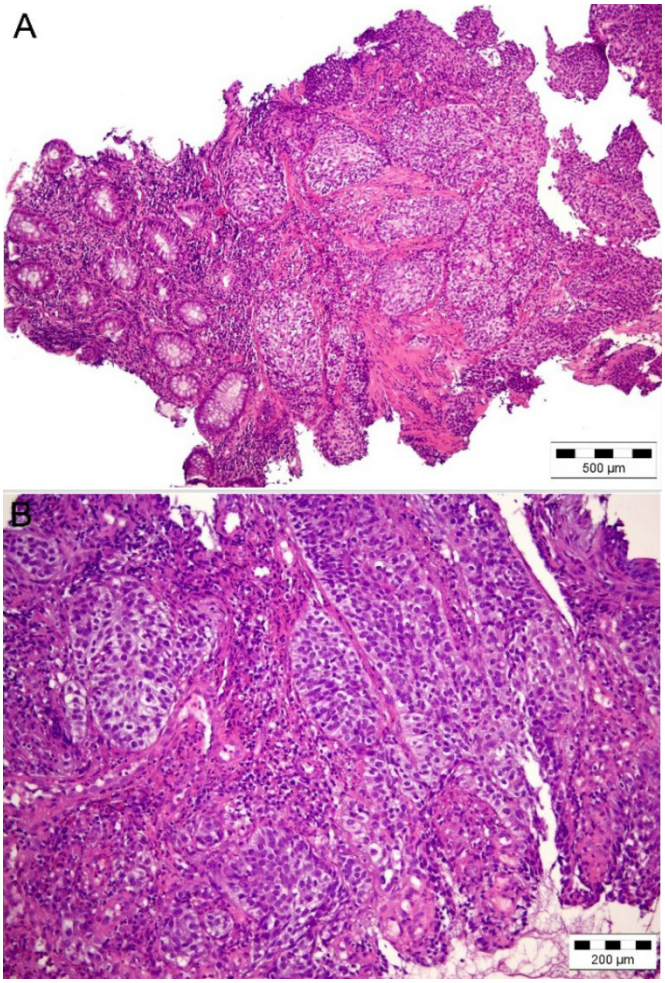
We present a diagnostically and therapeutically challenging case of locally advanced ASCC in a man living with HIV, exhibiting an unusual biomarker profile characterized by p16 overexpression, aberrant p53 expression, and an extremely high Ki-67 proliferation index, followed by rapid disease progression despite standard therapy.

Case Presentation

In September 2020, a 56-year-old man living with HIV, with a history of sexual contact with men, presented to the Institute for Oncology and Radiology of Serbia (IORS) with rectal bleeding and anal discomfort. He was on a stable antiretroviral therapy (ART) regimen (abacavir/dolutegravir/lamivudine), which he had been receiving since 2009. The patient had sustained virological suppression (undetectable HIV viral load) and adequate immune reconstitution (CD4+ count within normal range). There was no documented history of AIDS-defining illnesses.

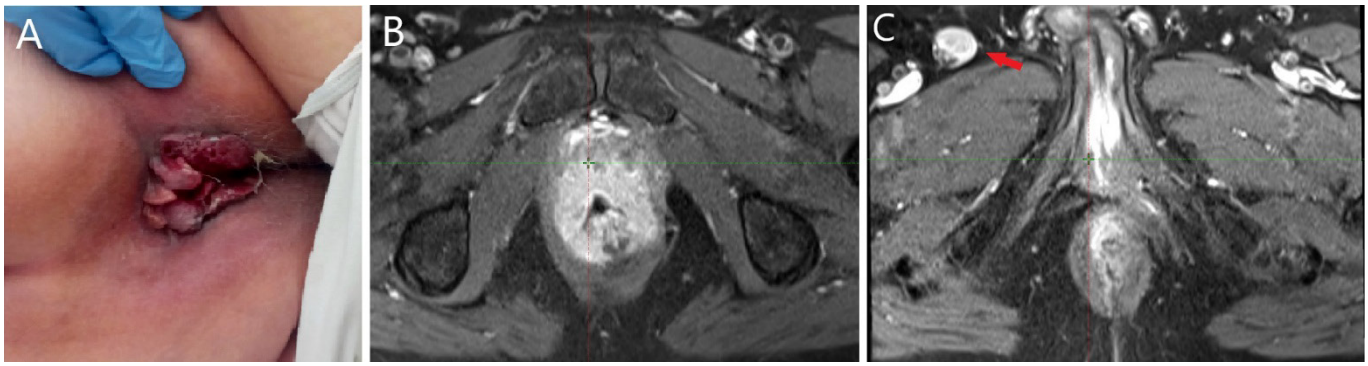
Initial diagnostic evaluation included pelvic magnetic resonance imaging (MRI), thoracoabdominal computed tomography (CT), and colonoscopy with biopsy. The tumor was clinically staged as T4N1cM0 (Figure 1) and histopathologically confirmed as moderately differentiated squamous cell carcinoma (Figure 2).

Figure 2. Histological characteristics.



A) Cancer infiltration of the anorectal mucosa (HE, ×100); **B)** Morphological features of non-keratinizing squamous cell carcinoma: large polygonal tumor cells with eosinophilic cytoplasm forming sheets (HE, ×200).

Figure 1. Clinical presentation and MRI findings.



A) Clinical presentation: a large exophytic tumor affecting the skin of the perianal region; **B)** Transverse magnetic resonance imaging (MRI): tumor mass involving the distal rectum and anus, with infiltration of the prostate, prostatic urethra, penile bulb, and bilateral pubococcygeal muscle; **C)** MRI showing lymphadenopathy in the right inguinal region (red arrow).

The patient was evaluated by an infectious diseases' specialist. Given his stable ART adherence, undetectable viral load, CD4+ count above 500 cells/μL, Eastern Cooperative Oncology Group (ECOG) performance status of 0, and unremarkable hematologic and biochemical parameters, the multidisciplinary tumor board (TB) at IORS determined that he was eligible for definitive chemoradiotherapy (CRT).

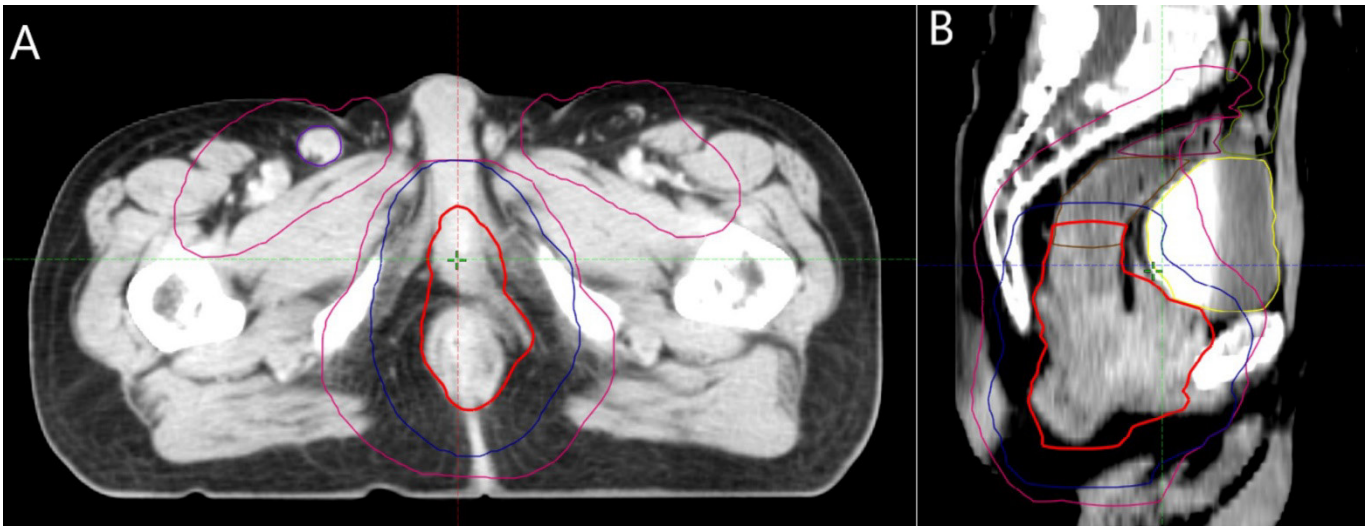
Radiotherapy (RT) was delivered using volumetric modulated arc therapy (VMAT). A total dose of 59.4 Gy was prescribed to the primary tumor, and 50.4 Gy to the pelvic and inguinal lymph nodes, both administered in conventional fractions of 1.8 Gy per day (Figure 3). Concurrent chemotherapy (CHT) consisted of two cycles of continuous infusional 5-fluorouracil (5-FU; 1,000 mg/m² on days 1–4 and 29–32) and mitomycin C (10 mg/m² on days 1 and 29), in accordance with national guidelines.

After receiving 11 fractions of radiotherapy (RT) totaling 19.8 Gy and the first cycle of chemotherapy (CHT), the patient developed treatment-related toxicities, including Grade 3 febrile leukopenia, Grade 2 radiodermatitis, and scrotal lymphedema, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [6]. Radiotherapy was temporarily suspended, and the patient received supportive care, including empiric antibiotics and granulocyte colony-stimulating factor (G-CSF). Upon hematologic recovery (leukocyte count > 3.0 × 10^9/L), RT was resumed. Two additional 14-day interruptions occurred due to a COVID-19 outbreak in the radiotherapy department; the patient himself remained uninfected. The overall treatment duration was 70 days, reflecting cumulative delays.

At the six-month post-treatment evaluation, pelvic MRI revealed post-radio chemotherapy fibrosis, a rectal wall defect adherent to the prostate, and a 9 × 9 mm nodular lesion suspicious for recurrence. Rectoscopy showed a fibrotic lesion with telangiectasia and a small umbilication toward the prostate, without definitive signs of fistula or tumor recurrence. Biopsy of the anal lesion demonstrated chronic fibrous inflammation without evidence of tumor infiltration. Based on these findings, no additional oncologic intervention was undertaken, and the patient continued routine surveillance.

At twelve months, clinical deterioration was observed, including pelvic pain, tenesmus, and discharge. Rectoscopy in May 2022 revealed a circumferential recurrent tumor involving the entire anal canal, with proximal extension into the rectum and an anterior wall fistulous tract. Following the multidisciplinary tumor board (TB) recommendation, an abdominoperineal resection was performed in June 2022. Early postoperative imaging (MRI and anoscopy) identified a urethroperineal fistula. Subsequent PET/CT in February 2023 demonstrated pelvic recurrence with bladder and prostate invasion, including a defect at the anorectal junction associated with an abscess, as well as pulmonary metastases. Systemic chemotherapy with 5-FU and cisplatin (CDDP) was considered according to NCCN guidelines [3], but rapid clinical decline and fistula-related complications precluded further cytotoxic therapy, and the patient was referred to palliative care.

Figure 3. Target volume delineation for radiation treatment planning.



Target volumes receiving 50.4 Gy are outlined in burgundy, and those receiving 59.4 Gy are outlined in blue. The gross tumor volume is marked in red on the CT simulation transfer section **(A)** and sagittal section **(B)**.

To better understand the tumor's biological behavior, archived tissue specimens from the initial biopsy were re-examined at the Institute of Pathology, University of Belgrade, with the patient's consent, using immunohistochemical analysis (Figure 4). The reevaluation focused on three key biomarkers: p16, p53, and Ki-67. Overexpression of p16 typically reflects transcriptionally active high-risk HPV infection with both etiological and prognostic implications. Aberrant p53 expression is often associated with TP53 mutations and correlates with aggressive tumor behavior and poor outcomes. A high Ki-67 proliferation index indicates increased tumor cell proliferation, also linked to adverse prognosis.

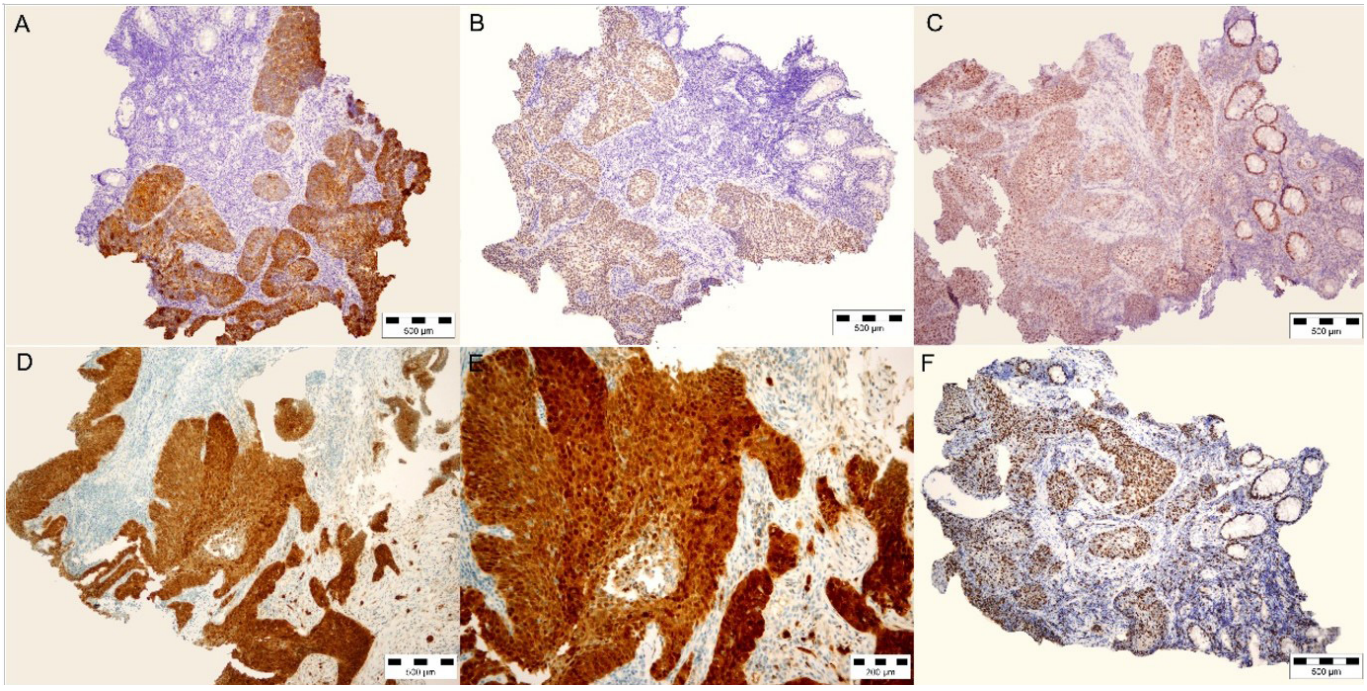
Immunohistochemistry confirmed squamous differentiation, demonstrated by positive CK5/6 and p40 staining (Figure 4A, B). The tumor exhibited diffuse moderate-to-strong nuclear p53 positivity (Figure 4C), consistent with aberrant p53 expression and a potentially aggressive, therapy-resistant phenotype. Strong and diffuse nuclear and cytoplasmic p16 expression was observed (Figure 4D, E), serving as a surrogate marker of transcriptionally active high-risk HPV. The coexistence of p16 positivity and aberrant p53 represents an uncommon immunophenotypic pattern, reflecting complex tumor biology. The Ki-67 proliferation index exceeded 99% (Figure 4F), indicating extremely high cellular proliferation and corroborating the aggressive clinical course observed.

Discussion

Treating people living with HIV (PLWH) diagnosed with anal squamous cell carcinoma (ASCC) presents substantial clinical challenges, particularly in the context of immune dysfunction. HIV-associated immunosuppression compromises immune surveillance, reducing the host's ability to clear oncogenic human papillomavirus (HPV) infections and facilitating progression to malignancy [7]. High-grade squamous intraepithelial lesions (HSIL), corresponding histologically to anal intraepithelial neoplasia grades 2 and 3 (AIN2/3) and representing direct precursors to ASCC, are detected in over 80% of cases among PLWH [7–9]. This high prevalence reflects the synergistic effect of persistent HPV infection and immunosuppression in this population [9].

According to the 2023 NCCN Clinical Practice Guidelines for anal carcinoma, treatment recommendations for PLWH mirror those for HIV-negative individuals, with concurrent chemoradiotherapy (CRT) remaining the standard of care regardless of HIV status, provided immune function is adequately preserved [3]. Khandwala *et al.* [10] similarly emphasize that standard CRT protocols

Figure 4. Immunohistochemical profile.



A) CK5/6 immunopositivity in infiltrating anal canal tumor (×100); **B)** p40 immunopositivity (×100); **C)** diffuse p53 immunopositivity (×100); **D)** strong nuclear and cytoplasmic p16 immunopositivity (×100); **E)** p16 immunopositivity at higher magnification (×200); **F)** diffuse Ki-67 expression (×100).

are applicable to PLWH, although advanced immunosuppression may necessitate careful monitoring and supportive care. PLWH with advanced immunosuppression, particularly those with CD4+ counts below 200 cells/μL, are at increased risk of acute treatment-related toxicities, such as mucositis and dermatitis, which frequently result in treatment interruptions or dose modifications. While the detailed characterization of these toxicities varies across studies, their clinical impact is well recognized and necessitates vigilant monitoring to maintain treatment intensity [3,10]. This is clinically significant, as higher radiation doses delivered with minimal treatment interruptions have been identified as key determinants of improved local control and overall survival [11].

Overall, PLWH and HIV-negative patients with ASCC demonstrate comparable response rates to treatment, likely due to shared molecular characteristics of most ASCC tumors [3,10]. Both clinical practice guidelines and observational studies support the application of standard concurrent chemoradiotherapy protocols across these patient groups, reflecting similar therapeutic efficacy despite differences in immune status.

A recent retrospective cohort study by Shing *et al.* analyzed survival in patients with anal cancer in the USA from 2001 to 2019 and reported higher adjusted all-cause and ASCC-specific mortality among PLWH compared to HIV-negative individuals, highlighting the increased mortality risk associated with HIV infection in this population [12].

HPV status remains a critical prognostic factor in ASCC. HPV-positive tumors are generally more sensitive to radiation and chemotherapy, often resulting in higher rates of complete response, improved locoregional control, and better overall and disease-free survival. In contrast, HPV-negative tumors are associated with poorer clinical outcomes across these measures [13].

While HPV and p16 status are well-established biomarkers in head and neck cancers, their utility in ASCC is still evolving. Although research continues to investigate their prognostic value in ASCC, p16 is widely accepted as a surrogate marker for high-risk HPV infection and is actively studied for its role in predicting treatment outcomes and aiding risk stratification [14].

A recent systematic review and meta-analysis by Parwaiz *et al.* emphasized the prognostic utility of several biomarkers in ASCC, including HPV positivity regardless of virus type and p16 expression. The study also highlighted the emerging significance of p53 mutation status, increasingly recognized for its potential role in predicting disease progression and treatment outcomes [14].

Furthermore, a recent review by Upadhyay *et al.* comprehensively addressed current treatment options for ASCC, emphasizing the potential role of HPV status as a prognostic marker for survival, recurrence, and treatment response. This review summarized emerging therapeutic strategies and highlighted the clinical relevance of HPV status in guiding personalized treatment approaches [15]. Upadhyay *et al.* also discussed emerging HPV-targeted therapies, including prophylactic vaccines and therapeutic vaccines targeting oncogenic proteins such as E6 and E7, which are currently under investigation in clinical trials for patients with metastatic ASCC [15]. However, molecular complexity within ASCC subtypes continues to be uncovered.

Moreover, Balci *et al.* assessed p53 expression by immunohistochemistry and reported that aberrant p53 expression was associated with an increased risk of local recurrence, even among patients with HPV-positive ASCC, suggesting that this prognostic effect may be at least partially independent of HPV status [16]. Similar findings were reported by Bruyère *et al*., who conducted uni- and multivariate analyses in a large cohort of HIV-negative patients with stage I–III anal canal carcinoma. Their study identified aberrant p53 expression, HPV/p16 negativity, age over 60, and advanced local stage (IIIa–c) as significant predictors of reduced progression-free and overall survival, with biomarker status demonstrating stronger prognostic value than traditional clinical factors [5]. Likewise, Gilbert *et al.* assessed p53 and p16 expression by immunohistochemistry and found them to be inversely correlated. Their study demonstrated that p16 negativity, often associated with aberrant p53 expression, was significantly linked to worse relapse-free and overall survival, reinforcing the prognostic relevance of p53 and its connection to HPV-related tumor biology [17]. Notably, aberrant p53 expression is more frequently observed in HPV-negative ASCC, which is often characterized by disruptive TP53 mutations and poor response to standard chemoradiotherapy [18].

In the present case, a distinct immunohistochemical profile was observed, characterized by aberrant p53 expression coexisting with p16 positivity. This discordant biomarker pattern is relatively uncommon, as aberrant p53 expression typically correlates with p16 negativity. Although such co-expression has been infrequently described in the

literature, its clinical significance remains uncertain. The tumor also demonstrated a markedly elevated Ki-67 proliferative index of 99%, which, in conjunction with the atypical biomarker profile, may indicate an aggressive biological phenotype; however, further research is required to substantiate this association.

While this comprehensive immunohistochemical analysis helped clarify the aggressive biological behavior of the tumor, it does not provide the full prognostic picture. The patient was diagnosed at a locally advanced stage (T4N1cM0), where long-term outcomes are generally poor despite high initial response rates, regardless of tumor subtype or molecular profile. As previously noted, p16 positivity serves as an etiological marker of transcriptionally active HPV infection, raising the question of whether earlier detection through screening could have improved this patient's prognosis. Given that the patient belongs to a high-risk population, PLWH and MSM, it is plausible that earlier screening might have been beneficial. However, organized HPV-related cancer screening programs in Serbia are primarily focused on cervical cancer in women aged 30 to 65, with no structured screening currently in place for high-risk male populations [19,20].

Furthermore, treatment-related complications, including severe acute toxicities, resulted in interruptions and a prolonged overall treatment duration, which may have adversely affected treatment response and clinical outcomes. Prolonged treatment time has previously been associated with reduced locoregional control and survival in ASCC patients receiving chemoradiotherapy [11]. This case also highlights broader systemic challenges in managing ASCC in PLWH, including increased susceptibility to toxicities, vulnerability to infections, and potential delays in care.

Despite growing interest in biomarker-driven approaches to ASCC, standardized risk stratification models integrating HPV status, p16/p53 expression, and host immunologic parameters are currently lacking. The findings from this case contribute to the limited but expanding body of evidence emphasizing the need for more nuanced prognostic tools and tailored therapeutic strategies in this population.

Conclusions

Effective management of anal squamous cell carcinoma (ASCC) in people living with HIV (PLWH) requires a comprehensive and individualized approach. Early detection through structured screening is essential, given the elevated risk associated with persistent HPV infection and HIV-related immunosuppression. Optimizing antiretroviral therapy (ART) enhances immune recovery and improves treatment tolerability and completion rates.

Tailored treatment strategies should incorporate detailed pathological and molecular profiling, including HPV status and expression patterns of key biomarkers such as p16 and p53. While p53 inactivation is common in HPV-associated ASCC, the prognostic implications of p16+/aberrant p53 co-expression, an unusual and potentially discordant pattern observed in this case, remain poorly defined. The co-expression of p16 and aberrant p53, together with a high Ki-67 index, may indicate an aggressive tumor phenotype not captured by conventional risk models.

This case underscores the need to refine biomarker-based risk stratification frameworks by incorporating complex immunohistochemical profiles. Future research should evaluate how such patterns influence disease progression and treatment response, particularly in immunocompromised populations. Additionally, prospective studies are warranted to determine whether standard chemoradiotherapy protocols require adaptation for PLWH to optimize both oncologic outcomes and treatment tolerability.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP). Approval was granted by the patient, who signed an informed consent for participation in this report. Signed form available upon request.

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Conflict of interest

No conflict of interest is declared.

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