

# Anal squamous cell carcinoma in HIV/AIDS patients in the HAART era: Report of 8 cases and literature review

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## Summary

**Background.** Anal squamous cell carcinoma is a rare neoplasm with a higher incidence in the HIV-seropositive population. **Patients and methods.** Epidemiologic, clinic, immunologic, virologic and therapeutic characteristics of 8 HIV-positive patients with anal squamous cell carcinoma were descriptively and retrospectively analyzed from 2005 to 2011. **Results.** Median of age of patients was 39 years, 75% were male and 83% were men who have sex with men. Median elapsed time from HIV infection to anal cancer diagnosis was  $10.5 \pm 9.5$  years. Anal pain and local large tumors detected by physical examination were the most common clinical manifestations; pain with or without itching was marginally correlated with poor survival. The median of CD4 T-cell count for the whole study group was 330 cells/ $\mu$ L. At the time of the neoplasm diagnosis, CD4 T-cell count was more than 200 cells/ $\mu$ L in 62.5% of the patients. In the descriptive analysis, higher CD4 T-cell count was significantly associated with a prolonged survival. In the overall population, 71% were receiving highly active antiretroviral therapy (HAART) and all of them had undetectable viral load at the time of neoplasm diagnosis. HAART was correlated with better survival in the overall population. Histopathologic examination showed that 4 cases (50%) had in situ carcinoma and 4 patients (50%) had diagnosis of invasive anal carcinoma. One patient underwent surgical tumorectomy plus HAART, 2 patients received chemotherapy plus HAART and 3 patients were treated with fractionated radiotherapy plus systemic

chemotherapy plus HAART. One patient died without the possibility of treatment due to his poor clinical condition and for one patient was no available data. After a follow up of 2 years, overall survival rate was 71%. **Conclusion.** A carefully evaluation of anal infiltrative or tumoral lesions is necessary to achieve an early diagnosis and to improve the survival in this kind of patients.

**Key words.** Anal cancer, anal squamous cell carcinoma, HPV, HIV, AIDS.

## Carcinoma escamoso de la región anal en pacientes con HIV/SIDA en la era de la HAART: Análisis de 8 casos y revisión de la literatura

### Resumen

**Introducción.** El carcinoma anal escamoso es una neoplasia rara pero con incidencia creciente en la población infectada por el virus de la inmunodeficiencia humana (VIH). **Pacientes y métodos.** Se analizaron de manera retrospectiva y descriptiva las características epidemiológicas, clínicas, inmunológicas, virológicas y terapéuticas de 8 pacientes VIH positivos con carcinoma anal escamoso asistidos entre los años 2005 y 2011. **Resultados.** La mediana de edad de los pacientes fue de 39 años, 75% fueron varones y 83% mantenían relaciones homosexuales. La mediana de tiempo transcurrido entre el diagnóstico de la infección por VIH y el de la neoplasia anal fue de  $10,5 \pm 9,5$  años. El dolor anal y las tumoraciones de gran tamaño detectadas en el examen físico fueron las manifestaciones clínicas más comunes. La mediana de CD4 al momento del diagnóstico de la neoplasia

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anal para la totalidad del grupo de estudio fue de 330 células/ul; 62,5% de los pacientes tuvieron recuentos de CD4 > 200 células/ul. En el análisis descriptivo, un conteo de CD4 alto se asoció de manera significativa con una supervivencia más prolongada. El 71% de la población total evaluada recibía terapia antirretroviral de gran actividad (TARGA o HAART por sus siglas en inglés) al momento del diagnóstico y todos ellos tenían carga viral plasmática indetectable. El uso de TARGA se correlacionó con una mejor supervivencia. El análisis histopatológico demostró 4 casos (50%) de carcinoma *in situ* y 4 pacientes (50%) fueron carcinomas anales invasores. Un paciente fue tratado con resección quirúrgica de las lesiones más TARGA, 2 recibieron quimioterapia y TARGA, y 3 fueron tratados con radioterapia en dosis fraccionadas más quimioterapia sistémica y TARGA. Un paciente falleció sin posibilidades de tratamiento debido a su condición clínica y de otro paciente no se obtuvieron datos del tratamiento. En el tiempo de seguimiento de 2 años la supervivencia global fue de 71%. **Conclusión.** Las lesiones perianales e intraanales con características infiltrativas deben ser cuidadosamente evaluadas en la población VIH positiva para alcanzar un diagnóstico precoz que mejore la supervivencia de este tipo de pacientes.

**Palabras claves.** Cáncer anal, carcinoma escamoso anal, HPV, HIV, SIDA.

#### Abreviaturas

HAART: Highly active antiretroviral therapy.

HIV: Human immunodeficiency virus.

HPV: Human papillomavirus.

ASCC: Anal squamous cell carcinoma.

AIDS: Acquired immunodeficiency syndrome.

HCV: Hepatitis C Virus.

MSM: Men who have sex with men.

IDU: Intravenous drug users.

ISAC: *In situ* anal carcinoma.

IVAC: Invasive anal carcinoma.

AIL: Anal intraepithelial lesion.

The widespread use of highly active antiretroviral therapy (HAART) since 1996 has dramatically reduced the incidence of opportunistic infections and certain AIDS-defining neoplasms in human immunodeficiency virus (HIV) seropositive patients.<sup>1</sup> The incidence of Kaposi's sarcoma and certain subtypes of Non-Hodgkin's lymphomas (especially primary central nervous system lymphoma) declined 70%.<sup>2</sup> However, HIV-infected people also have an increased risk of non-AIDS defining cancers in-

cluding those associated with previous viral coinfections as anal cancer related with human papillomavirus (HPV) infection, liver cancer associated with hepatitis B and C viruses (HBV and HCV) and Hodgkin's lymphoma associated with Epstein-Barr virus infection. Also, lung cancer shows a high incidence in the HIV/AIDS population, related to the high incidence of cigarette smoking.<sup>3,4</sup>

Here we analyzed the clinical features, treatment and outcome of a cohort of 8 HIV-seropositive patients assisted in a single center of Buenos Aires, Argentina, with diagnosis of anal squamous cell carcinoma (ASCC).

#### Patients and methods

We performed a descriptive and retrospective analysis of the epidemiological, clinical, histopathological, immunological and virological findings and the outcome of 8 patients with AIDS and ASCC assisted at a single reference hospital of infectious diseases in Argentina from 2005 to 2011. The patients were clinically staged based on clinical, proctologic, histological and radiological findings. Physical examination, including performance status, complete blood cell counts, serum biochemistry, CD4 T cell counts, HIV plasma viral load and hepatitis C (HCV) serology were performed in all the patients. In order to define the neoplasm extension, all patients underwent the following studies: chest X-ray and complete tomography scan of thorax, abdomen and pelvis. In all cases, a rectoscopy was made and multiple biopsy smears of the lesion were performed. Diagnosis was confirmed by the histopathological examination of the biopsy smears. Histopathological biopsy smears were classified as *in situ* anal carcinoma (ISAC) or invasive anal carcinoma (IVAC). Therapeutics modalities included HAART, radiotherapy alone, radiotherapy plus chemotherapy and surgery. We have also evaluated the response of chemotherapy regimen based on Nigro scheme (5-fluorouracil plus mitomycin C), the response to 3D-radiotherapy and the outcome. Finally, we included the overall survival rate during a follow up of 2 years.

#### Results

Eight patients with histopathological diagnosis of ASCC were included in the study population. Median of age was 39 years (range: 35 to 58 years), 75% were male and 83% were men who have sex with men (MSM). Demographic features are included in Table 1. Median elapsed time from HIV diagnosis and anal cancer diagnosis was 10.5 ± 9.5 years (range: 0 to 26 years). Even though the wide range, no outliers were detected through extre-

**Table 1.** Demographic findings of eight patients with in situ and invasive anal squamous cell carcinoma in HIV/AIDS patients.

	1	2	3	4	5	6	7	8
<b>Gender</b>	Female	Male	Male	Male	Male	Male	Male	Female
<b>Age</b>	35	39	39	41	49	58	40	38
<b>HIV/risk infection</b>	Unprotected sexual contact	Unprotected sexual contact	Unprotected sexual contact	Unprotected sexual contact	Unprotected sexual contact	Unprotected sexual contact	Unprotected sexual contact	Unprotected sexual contact
<b>HCV</b>	(-)	(+)	(+)	(+)	(-)	(-)	(-)	(-)

me studentized deviate tests. Elapsed time from both diagnosis was not correlated with survival neither at 5 years nor at the median time of 10.5 years ( $P = 0.67$  and  $P = 0.69$ , respectively). Anal pain and local large tumors (excluding anal warts) detected by physical examination were the most common clinical manifestations; pain with or without itching was marginally correlated with poor survival.

The median of CD4 T-cell count for the whole study group was 330 cells/ $\mu$ L (range: 17 to 1573 cells/ $\mu$ L); 62.5% of patients had a CD4 T cell count higher than 200 cell/ $\mu$ L at the time of the neoplasm diagnosis. However, an outlier patient was identified by Grubbs' test. Excluding this patient, from the final analysis yielded, the median of CD4 T-cell was 221.5 cells/ $\mu$ L. Even though the small size of the study group, in a descriptive analysis higher CD4 T-cell count was significantly associated with a prolonged survival. None of the patients presented

distance metastases. In the overall population study, 71% were receiving HAART and all of them had undetectable viral load at the time of ASCC diagnosis. Histopathologic examination showed that 50% had ISAC and 50% had IVAC. In a descriptive analysis, the use of HAART was correlated with prolonged survival. Three patients (37.5%) had antibodies to HCV. Coinfection of HIV with HCV was not associated with poor outcome. We could not identify other potential risk factors for poor outcome. One patient underwent surgical tumorectomy plus HAART, 2 patients received chemotherapy plus HAART and 3 patients were treated with fractionated radiotherapy plus systemic chemotherapy and HAART. For one patient there was no available data and other patient died without treatment possibility due to his poor clinical condition. During the follow up of 2 years, overall survival rate was 71% (Table 2).

**Table 2.** Immunological, histopathological and virological findings of eight cases of in situ and invasive anal squamous cell carcinoma in HIV/AIDS patients.

	1	2	3	4	5	6	7	8
<b>CD4 level (cells/<math>\mu</math>L)</b>	288	140	17	642	155	373	362	1,573
<b>HAART</b>	yes	no	ND	yes	no	yes	yes	yes
<b>Viral load</b>	undetectable	detectable	ND	undetectable	detectable	undetectable	undetectable	undetectable
<b>Histopathology</b>	ISAC	IVAC	ISAC	ISAC	ISAC	IVAC	IVAC	IVAC
<b>Treatment</b>	Surgery	NO	ChT plus HAART	ChT plus HAART	ChT plus RT plus HAART	ChT plus RT plus HAART	ND	ChT plus RT plus HAART
<b>Survival</b>	Alive	Dead	Dead	Alive	Alive	Alive	ND	Alive

ND: no data, ISAC: in situ anal carcinoma, IVAC: invasive anal carcinoma, ChT: chemotherapy, HAART: highly active antiretroviral therapy, RT: radiotherapy.

## Discussion

The incidence of AIDS-defining cancers declined gradually since 1996 with a subsequent increased incidence of non-AIDS defining cancers especially in AIDS patients older than 40 years. This increased incidence rates was observed for some of these cancers.<sup>5, 6</sup> HIV-infected patients show an increased risk of lung cancer, anal cancer, liver cancer and Hodgkin's lymphoma.<sup>1, 7</sup> The risk is increased 3-fold for lung cancer, 5-fold for liver carcinoma, 11-fold for Hodgkin's lymphoma and 29-fold

for ASCC.<sup>7</sup> Of these four neoplasms, the highest increase was observed for ASCC, especially among MSM.<sup>4, 8</sup> The high incidence of these neoplasms is independent of the widespread use of HAART as we could see in our series. All patients included in this analysis were diagnosed between 2005 and 2011 in the post-HAART era.

The high incidence of anal canal cancer is not exclusively of MSM; women with high grade cervical lesions or cervical and vulvar cancers associated with HPV oncogenic subtypes also have a high-risk for the development

of anal cancer.<sup>9</sup> HIV-seropositive women have also a high risk of abnormal cervical cytology in comparison with HIV-seronegative women.<sup>9, 10</sup> Two patients of our series were women and one of them with a history of vulvar and cervical cancer.

Anal carcinoma is a rare malignancy accounting only 1.6% of the gastrointestinal tract cancer in USA. ASCC is the most common histopathological subtype among the tumors that involve the anal canal. ASCC is not included as an AIDS-defining malignancy, but its incidence is increased in HIV-seropositive patients. Generally this malignancy appears after a long period of HIV infection; in this series, the median of time between HIV diagnosis and anal carcinoma was 10.5 years. However, presence of perianal or intraanal infiltrative lesions should be considered a reason to investigate this condition related with HIV infection. More than 90% of anal cancers are caused by HPV infection, especially the oncogenic subtype HPV16.<sup>11</sup> Previous studies showed that HAART has not reduced the prevalence of HPV infection and has not declined the incidence of high grade anal squamous epithelial lesions or ASCC, especially in MSM.<sup>12</sup> There is a strong association between oncogenic subtypes of HPV with cervical, vulvar and anal cancer. In this aspect, anal cancer is actually considered as a sexually transmitted disease, related with the history of anal warts due to HPV infection with oncogenic subtypes 16 and 18.<sup>13</sup> Risk of anal cancer is increased in receptive anal intercourse individuals of any gender, independently of HIV status and the grade of immunosuppression.<sup>14</sup>

Most cases of anal cancer (85%) occur in the anal canal and these carcinomas are characterized by aggressive local invasion that may involve the sphincter muscles. Clinical presentation includes anal pain, proctorrhagia, anal abscess with fistulae and exophytic and infiltrative lesions that can compromise the perianal skin and the anal canal.<sup>15</sup> When the patients report pain or painful defecation, compromise of sphincter muscles is highly probable. In this case series, pain with or without itching was marginally associated with poor survival, probably as a surrogate of more extended local invasion. Diagnosis methods include anal inspection, digital examination, 3-D endoanal ultrasound and high resolution anoscopy. Computed tomography or magnetic resonance of abdominal cavity is necessary to detect the presence of metastases in regional lymph nodes.<sup>16, 17</sup> ASCC is one of the non-AIDS defining cancers that is not associated with CD4 T cell counts. In our experience, CD4 T-cell count was more than 200 cells/ $\mu$ L in 5 patients (62.5%) at the time of neoplasm diagnosis. In our series, a higher CD4

T-cells count was correlated with better overall survival rates after excluding an outlier patient from the final analysis model.

HPV infection with oncogenic subtypes is the most important risk factor to develop anal carcinoma. Palefsky et al<sup>18</sup> evaluated 357 patients HIV seropositive MSM with anal cytology test to detect HPV infection, high resolution anoscopy and biopsy for detection of anal intraepithelial lesions (AIL); 81% of the patients had AIL of any grade; 52% had AIL-2,3 and 95% of patients had cytological signs of HPV infection. HIV patients, especially MSM should be evaluated with anoscopy and anal cytology at least every 6 months independent of CD4 T cell count, viral load and HAART. In a cohort study that included 247 HIV-seropositive MSM receiving HAART, de Pokomandi et al<sup>19</sup> confirmed the high prevalence of AIL-2,3 in this population, even if they received HAART. In that study, predictive factors to develop AIL-2,3 and anal carcinoma included infection by oncogenic subtypes (especially HPV 16) and infection due to multiple subtypes of HPV.<sup>20</sup>

In our series, most patients presented with perianal and intra-anal infiltrative lesions that motivated biopsy smears. Presence of anal infiltrative lesions should be evaluated by anoscopy and multiple biopsy smears should be obtained. Our decision to obtain multiple biopsies smears was based on the probability to observe a different grade of histopathological lesions and the indirect signs of HPV infection (koilocytes). In our series, histopathological examination showed that 50% of the patients had ISAC and 50 % had IVAC.

Treatment of ASCC has changed in the last 20 years and actually is considered as a model of organ-preservation treatment. Concurrent chemoradiotherapy is the standard treatment for ASCC. Chemotherapy is based on mitomycin-C (10 mg/m<sup>2</sup>) as intravenous bolus on day 1 only, with 5-fluorouracil (5-FU) (1,000 mg/m<sup>2</sup>) over 24 hours in days 1 to 4 according to Nigro's scheme.<sup>21</sup> HAART should be included as part of the treatment in all the patients.<sup>22</sup> In the majority of cases, preservation of anal muscle sphincter is possible due to the efficacy of combined chemoradiotherapy, with 55% to 75% of survival rates and preservation of anal sphincter in 60% to 90% of the patients, independent of the neoplasm stage.<sup>21,22,23</sup> Numerous retrospective reviews confirm that combined chemoradiation is the treatment of choice for patients with diagnosis of ASCC in terms of local control of the neoplasm disease and the sphincter preservation.

Vatra et al<sup>24</sup> et al compared 20 HIV-seropositive patients with 24 HIV-seronegative subjects with diagnosis



of ASCC. Survival rates at one year after chemotherapy with preserved anal sphincter were 85% in the HIV-seronegative in comparison with 48% in the HIV seropositive ( $P < 0.05$ ). At three years, the median survival in HIV-seropositive patients was 18 months significantly shorter than the 28 months observed in the HIV-seronegative individuals ( $P < 0.001$ ). Also, in this study, T CD4 cell count less than 250 cells/ $\mu$ L at the time of the neoplasm diagnosis was a predictive factor of poor prognosis and a shorter survival. In our series, a higher CD4 count was correlated with better overall survival rates after excluding an outlier patient from the final analysis model. In patients under HAART with undetectable viral load and immune reconstitution, chemotherapy can influence on the CD4 T cell count levels and it is possible that during the treatment some patients may present decreasing number of CD4 T cell count. In the other hand, generally, there was no change in the plasma viral load.<sup>21</sup> In our series, a descriptive analysis showed that the use of HAART was correlated with prolonged survival.

This study is a single hospital analysis of anal cancer in HIV-seropositive patients and our findings should not be generalized. Several strengths of our series should be mentioned, as the multidisciplinary approach by oncologists, pathologists and infectologists in a highly specialized hospital. Besides, to our knowledge, this case series is the first analysis of anal cancer in HIV-seropositive subjects in Argentina. There are obvious limitations to this study, including its retrospective nature and the obvious absence of a control group. The small size of the cohort and the characteristics of a single center of infectious diseases should be included as other limitations.

A higher suspicion is necessary to achieve an early diagnosis and to improve the survival of these patients. The high rates of tumor recurrence observed especially in HIV-seropositive patients, carry out necessary a carefully evaluation of anal infiltrative or tumoral lesions in this kind of patients.

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