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A Case Series of Therapeutic Outcomes of Head and Neck Cancer Patients with Unnoticed HIV Infection

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Abstract

Background: Immune suppression secondary to Human Immunodeficiency Virus (HIV) infection is associated with an increased risk of head and neck cancer (HNC) and poorer tumor-related survival. In this article, the authors focused on the outcome of a specific subgroup of HIV-HNC patients with undetectable HIV load at cancer diagnosis.

Case Presentation: We report of 4 HIV patients with head and neck cancer. The first patient showed an incidental finding of synchronous papillary thyroid carcinoma in the cervical lymph nodes after neck dissection. The second patient developed multiple local and regional recurrences of a nasal carcinoma. The third patient could not receive treatment for nasopharyngeal carcinoma due to multiple comorbidities. The fourth patient showed a long disease free survival after aggressive treatment of an oropharyngeal carcinoma. The patients reported developed synchronous HNC and local recurrences. Moreover, local control was not always easy to achieve. Multiple comorbidities, psychological factors and complications often led to treatment delay.

Conclusions: The authors suggest consideration of early aggressive treatment and intensive follow up for HIV-HNC patients despite undetectable HIV load; since other parameters, such as immunosuppression, inflammation and direct viral oncogenic effect, could have already accelerate the natural course of the disease and affect the outcome.

Keywords: Head and Neck Neoplasms; HIV; Immunology; Prognosis

Background

Immune suppression secondary to Human Immunodeficiency Virus (HIV) infection is associated with an two to five fold risk of head and neck cancer (HNC) [1]. In one case series with 94 HIV patients with head and neck cancer (HIV-HNC), patients with lower CD4 cell count at time of cancer diagnosis (<200 cells/μL) had significantly poorer survival. All but one patient had detectable HIV viremia at diagnosis [2].

In this article, the authors focused on the outcome of a specific subgroup of HIV–HNC patients with undetectable HIV load at cancer diagnosis. We report 4 HIV-HNC patients (Table 1, 2 and 3) who received cancer treatment from 2007 until 2017 at the Department of Otorhinolaryngology of the Medical University of Innsbruck, Austria. Data were obtained in a retrospective way from medical records. Diagnostic and therapeutic procedures were accorded in a multidisciplinary tumor board (MDT). HIV load and CD4 cell count at highly active combination anti-retroviral therapy (cART) initiation and at cancer diagnosis are described in table 1.

Case Presentation

Case 1: A 52-year-old non-smoking male homosexual patient was diagnosed with HIV infection in March 2014, stage C3. At that time, the patient had been treated with primary chemoradiotherapy due to an anal carcinoma cT2N1M0. After developing seborrhoic dermatitis, serologic tests revealed infection from HIV-1, subtype B.

In December 2015, the patient was subjected to total laryngectomy with bilateral selective neck dissection due to a Human papilloma virus (HPV)-negative cT3N0M0 laryngeal squamous cell carcinoma of the glottis (Figure. 1). In the surgical neck specimens, no cervical metastases from the SCC were found. However, there was an incidental finding of papillary thyroid carcinoma metastasis in 3 neck lymph nodes. The patient underwent total thyroidectomy 2 weeks later. The surgical specimen revealed a pT1a multifocal, papillary micro carcinoma of the thyroid gland. No complications were observed in the postoperative follow-up. Currently, the patient is free of disease.

Case No	1	2	3	4
Age*/Sex	52/Male	47/Male	54/Female	50/Male
Comorbidities	Hepatitis B	Hepatitis B	Hepatitis C, cardiac arrhythmia, bipolar disorder, renal insufficiency	None
CD4†/HIV RNA‡; §	21/4.90	87/4.23	703/0.67	44/5.88
CD4†/HIV RNA‡; II	245/<1.70	600/<1.70	<250/<1.70	146/<1.70
<250 CD4†; ¶	21	0	72	45
Tumor Site	Larynx	Nose	Nasopharynx	Oropharynx
HPV/p16	Negative	Negative	Unavailable	Negative
cTNM	T3N0M0	T2N0M0	T4N1M0	T4aN2bM0

*Years; †cell count/μL; ‡log10 copies/ml; § at cART initiation; II at cancer diagnosis; ¶ time (in months) of less than 250 CD4 cells/μL direct before cancer diagnosis;

Table 1. Patients' demographic and tumor characteristics

Case No	Primary treatment	Specific disease characteristics	Specific treatment related event
1	Laryngectomy and bilateral SND* II-IV	2nd primary	2nd primary
2	Partial nasal ablation	Perineural and lymphovascular spread	Repeated R1 Resections
3	None due to multiple comorbidities	None	None
4	Tumor resection, left MRND†, right SND*	None	R1 Resection; Acute abdomen

* Selective neck dissection; † Modified radical neck dissection;

Table 2. Treatment course of the disease

Case No	Further course	Relapse §	Survival §
1	Total thyroidectomy	No relapse II	21 II
2	1. Diagnostic cervical lymph node exstirpation in level Ib 2. Hyper-fractionated radiotherapy of primary tumor region, right cheek and right level Ib 3. Tumor resection of nasion and oral vestibule 4. Rest nasal ablation with resection of both frontal beaks and ethmoidal cells 5. Chemotherapy	5	34
3	Refusal of treatment	No treatment	17
4	1. Adjuvant RCTH ‡ 2. Chemotherapy	26	30

† Modified radical neck dissection; ‡ chemoradiotherapy; § in months; II until December 2017

Table 3. Further course and outcome of the disease

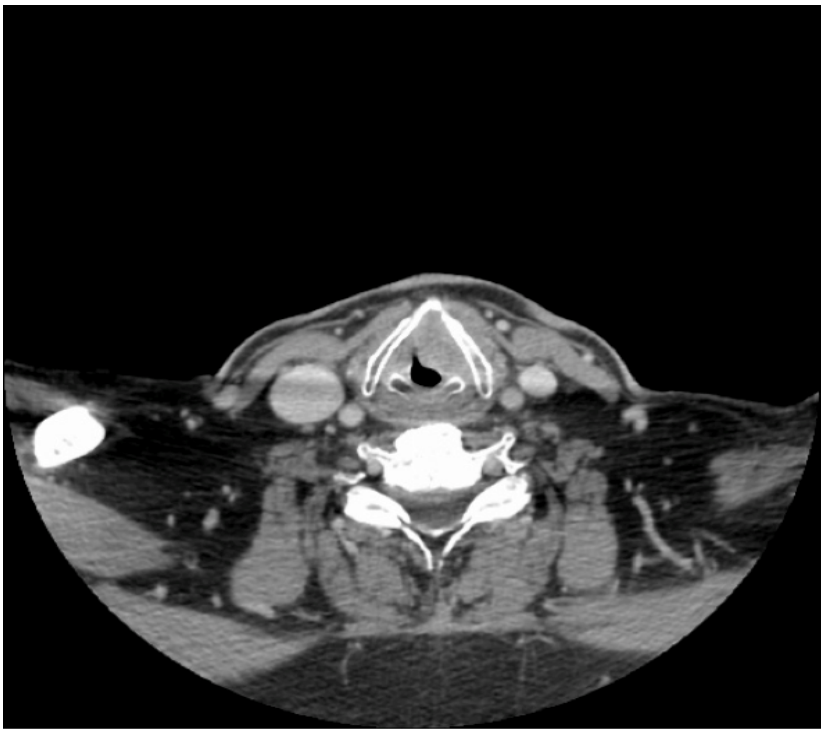

Figure 1. CT scan showing tumor of the left vocal cord.

Case 2: A 47-year-old smoking male homosexual patient was diagnosed with HIV infection in February 1992. In March 1999, he developed esophageal candidiasis. At that time, his HIV infection stage was C3. In October 2014, the patient was subjected to partial right nasal ablation due to an HPV-negative cT2N0M0 nasal squamous cell carcinoma. Because margins were not tumor-free, 4 further quite extensive resections in the midface (Figure. 2; left) of clinically uninvolved, but histologically positive tissue were performed.

To cope with histologic perineural spread and lymphovascular invasion, the patient underwent percutaneous hyperfractionated radiotherapy of the primary tumor region with 70.2 Gy from April 2015 until June 2015. During radiotherapy the patient developed a right cheek in transit metastasis as well as lymph node metastasis in the right level Ib and the radiation field was expanded accordingly. Following treatment, CT scans did not reveal any local or regional residual disease.

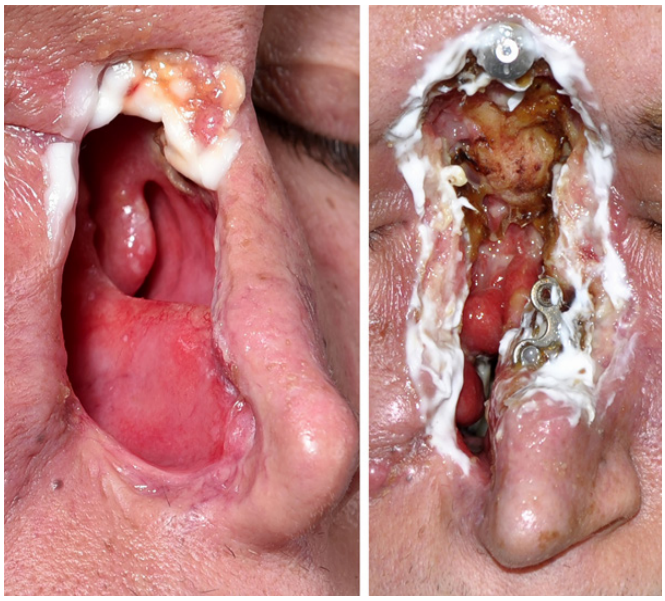

Figure 2. Left. Patient's midface after right partial nasal ablation with resection of the right nasal bony and cartilaginous pyramid, lobule and anterior septum and after 4 further resections.
Right. After right residual nasal ablation with resection of the left bony and cartilaginous nasal pyramid, as well as resection of both frontal beaks and ethmoid cells. Visible metal prosthesis for preliminary care with nasal epithesis.

Case 3: A 54-year-old smoking female patient was diagnosed with HIV infection in June 1986, stage C3. The virus was transmitted through intravenous drug use. In June 2015, the patient was diagnosed with a cT4N1M0 nasopharyngeal squamous cell carcinoma (Figure. 3). HPV status was unavailable. The patient could not receive primary chemoradiotherapy due to multiple comorbidities, such as liver cirrhosis, hepatitis C, cardiac arrhythmia, renal insufficiency, marasm (BMI 11.7) and bipolar disorder. Thus, primary radiotherapy was recommended in an attempt to obtain local tumor control. The patient refused to undergo radiotherapy, considering the possible complications. The patient deceased in October 2016.

Case 4: A 50-year-old smoking male homosexual patient was diagnosed with HIV infection in October 2003, stage C3. In July 2007, the patient was diagnosed with an HPV-negative cT4aN2bM0 oropharyngeal squamous cell carcinoma (Figure. 4). In August 2007, the patient was subjected to primary tumor resection. Margins were not tumor free. However, the patient developed acute abdomen due to appendicitis postoperatively.

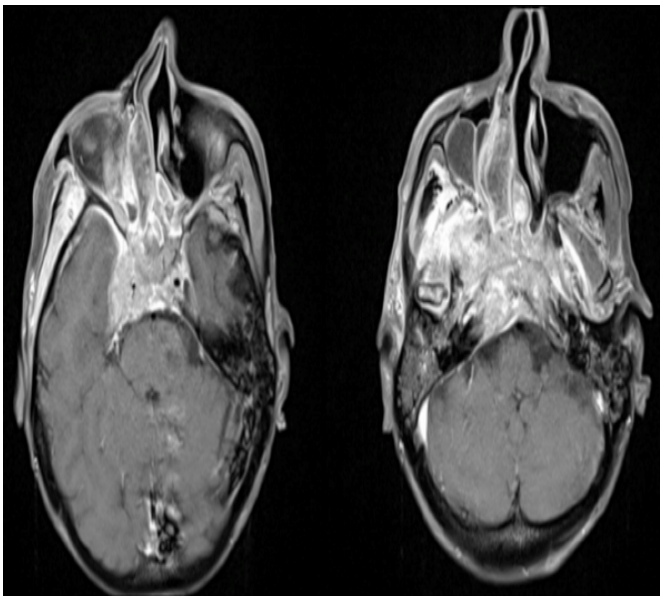

Figure 3. MRI scans show the infiltration of the nasopharyngeal carcinoma in the right maxillary sinus, the orbit, the optic nerve, the right retropharyngeal space and the anterior skull base. Left. Level of the orbit; Right. Level of maxillary sinus.

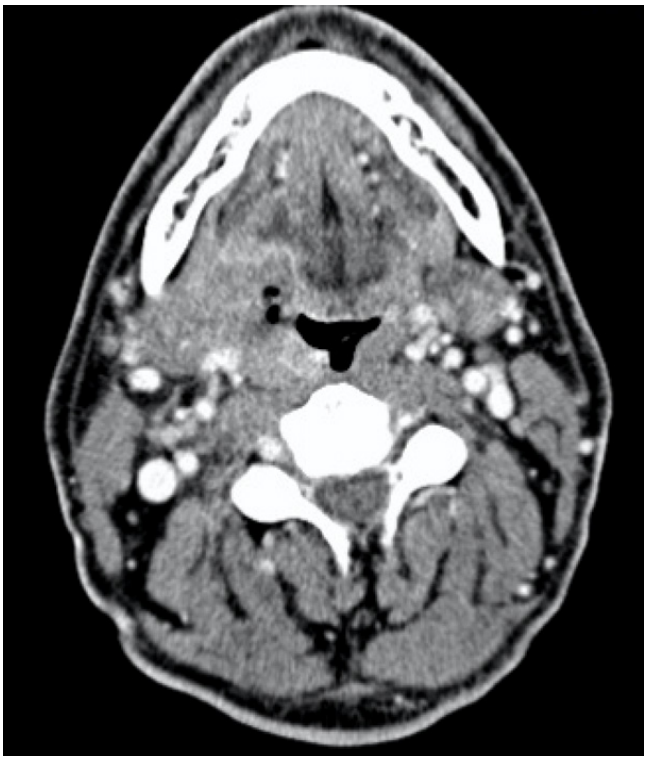

Figure 4. CT scan of the head and neck shows the infiltration of the oropharyngeal carcinoma in the parapharyngeal space, deep tongue muscles and mandible.

A right hemicolectomy was performed due to toxic megacolon and intestinal pneumatosis. Three weeks later, the patient underwent left modified and right selective neck dissection. TNM stage was pT4aN0M0R1. Further resection of the primary tumor was not possible. The patient underwent adjuvant chemoradiotherapy. In November 2007, there was no histologic or radiologic sign of malignancy or residual disease. In January 2010, he developed pleural metastases. Palliative chemotherapy with cetuximab and cisplatin was performed. The patient deceased in May 2010.

Discussion and Conclusions

This case series describes the unfavorable course of 4 HIV-HNC patients with undetectable HIV load. The patients reported here developed synchronous HNC and local recurrences. Moreover, local control was not always easy to achieve due to tumor positive margins and the existence of clinically uninvolved, but histologically positive tissue. Multiple comorbidities, psychological factors and complications often led to treatment delay. HIV-infected individuals have increased exposure to tobacco, alcohol and HPV infection, the three primary HNC risk factors [3]. Interestingly, 3/4 patients reported here were HPV-negative; HPV status was unavailable for 1/4 patient. 3/4 patients were smokers.

Immune suppression secondary to HIV infection is associated with an two to five fold risk of HNC [1]. Brickman and coauthors suggested that this increased risk could be attributed to immunosuppression, systemic inflammation and direct oncogenic effects [3]. Impaired lymphocyte function due to HIV infection results in decreased tumor surveillance and increased risk of malignancy. This link is stronger in Acquired immunodeficiency syndrome (AIDS) defining malignancies. The relationship between immunosuppression and the risk for non-AIDS defining malignancies (NADMs) such as HNC is less clear. Recent studies have detected an association between increased risk for NADMs and low CD4 count at cancer diagnosis, CD4 nadir and duration of low CD4 count [4, 5]. Particularly, patients with less than 200 CD4 cells/μL at initiation of cART and less than 250 CD4 cells/μL 2 years after cART had an increased risk for NADM and death due to NADM [4]. Bruyand and coauthors observed that a higher incidence of NADMs was independently associated with longer and current exposure to less than 500 CD4 cells/μL, but not to plasma HIV RNA level [5]. Also, in a case series with 94 HIV-HNC patients, patients with lower CD4 cell count at diagnosis (<200 cells/μL) had significantly poorer survival. All but one patient had detectable HIV viremia at diagnosis [2]. In our case series, all but one case had less than 150 CD4 cells/μL and higher than 3.50 log10 copies/ml HIV RNA at cART initiation (table I). Also, all cases had undetectable HIV RNA and all but one case less than 250 CD4 cells/μL at cancer diagnosis (table I).

During treatment, one patient also had less than 200 CD4 cells/μL and undetectable HIV RNA (case 2). It's already mentioned that HIV-associated immunosuppression could lead to initial carcinogenesis. Perhaps, long exposure to low CD4 cell count (<250 cells/μL) before cancer diagnosis could better describe the term immunosuppression and its importance on poor outcome. It's possible that HIV-associated immunosuppression may result in initial viral carcinogenesis (through infection or mutations) that cannot be reversed by immune reconstitution. Moreover, increased risk for NADMs due to long-lasting immunosuppression may not be detectable by CD4 count alone. Smoking could also lead to poorer outcome, as well as HIV-related comorbidities [2]. The role of HIV load on outcome remains unclear.

People living with HIV have been linked to elevated inflammatory markers compared to HIV-non-infected individuals even after years of detectable immune suppression [6]. In a large longitudinal cohort, Borges and coauthors detected a small but statistically significant association between interleukin-6, C-reactive protein and D-dimer and the hazard of developing infection-related and infection-unrelated malignancies [7].

Direct oncogenic effects have been linked to the HIV transactivator protein tat. This protein is secreted from HIV-infected cells and taken up by adjacent cells; it is involved in the activation of viral and cellular genes and in downregulation of DNA repair pathways, cell-cycle stimulation and inhibition of apoptosis [8]. The protein tat also appears to enhance the transformation and infectious potential of oncogenic viruses; it upregulates the expression of the HPV oncogenic proteins E6 and E7, thus enhancing the oncogenic potential of HPV [9]. Thus they may develop NADMs, including HNC [1].

Concluding, the authors suggest consideration of early aggressive treatment, increased vigilance and intensive follow up of HIV-HNC patients despite undetectable HIV viremia; since other parameters, such as immunosuppression, inflammation and direct viral oncogenic effect, could have already accelerate the natural course of the disease and affect the outcome.

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