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Case Report

Case Reports of Two Organ Transplanted Patients with Human Papillomavirus (HPV) Positive Oropharyngeal Squamous Cell Carcinoma Having Had Liquid Biopsy for Circulating Cell-Free HPV-DNA

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Abstract

Background and Aim: Human papillomavirus positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC), where tonsillar and base of tongue squamous cell carcinomas (TSCC and BOTSCC) dominate, all have better clinical outcome than HPV negative (HPV-) OPSCC, with current chemoradiotherapy. However, not all patients fare well. To gain more insight into treatment response, we are presently evaluating the presence of cell-free HPV DNA (cfHPV-DNA) in plasma collected before, during, and after therapy in patients with HPV+ OPSCC and correlating cfHPV-DNA levels with clinical characteristics and treatment response. Here we present case reports of two organ transplanted patients included in that study.

Material and Methods: A kidney transplanted patient with an HPV-type 16 (HPV16) positive BOTSCC, and a liver transplanted patient with an HPV-type 33 (HPV33) positive TSCC, were initially followed for presence of cfHPV-DNA with droplet digital PCR (ddPCR) assaying for HPV16 or 33 respectively.

Results and Conclusion: Both patients, were cfHPV-DNA positive at diagnosis, but neither had remarkably high cfHPV-DNA levels at that time point. The kidney transplanted patient with a BOTSCC, failed to respond to treatment, exhibited rising cfHPV-DNA levels throughout the observation period and died shortly after completing primary treatment due to progressive disease. The liver transplanted patient with a TSCC, provided only a diagnostic sample for ddPCR and died without presenting progressive disease, after completing treatment.

To conclude, both solid organ transplanted patients fared poorly and had difficulties tolerating therapy.

ABBREVIATIONS

Cfhpv-DNA: Cell Free HPV DNA; CRT: Chemoradiotherapy; CT: Computed Tomography; Ddpcr: Digital Droplet PCR; HNSCC: Head and Neck Squamous Cell Carcinoma; HPV: Human Papillomavirus; OPSCC: Oropharyngeal Squamous Cell Carcinoma; RT: Radiotherapy; TSCC: Tonsillar Squamous Cell Carcinoma

INTRODUCTION

Human papillomavirus (HPV) is a well-established risk factor for oropharyngeal squamous cell carcinoma (OPSCC), where tonsillar and base of tongue squamous cell carcinoma dominate (TSCC and BOTSCC) and are rising epidemically in incidence in many countries [1-13]. HPV-positive (HPV^+) OPSCC responds more readily to treatment compared to HPV-negative (HPV^-) OPSCC, but still not all patients are cured since approximately 20% of the patients encounter a relapse or do not respond to treatment [1-3,11-14]. To gain more knowledge regarding response to therapy, in an ongoing study we are evaluating the presence of cell-free HPV DNA (cfHPV-DNA) in plasma at diagnosis, during, and after treatment at regular follow-ups in patients with HPV^+ head and neck squamous cell

carcinoma (HNSCC), analogous to that done by others in HPV⁺ cancer [15-20]. In this ongoing study in Stockholm, Sweden most patients had an HPV⁺ OPSCC, and the cfHPV-DNA levels of the patients at different time points are being correlated with their clinical characteristics, and treatment response. Here we present two case reports from that study of two solid organ transplanted patients that unfortunately did not fare well.

PATIENTS

The two solid organ transplanted patients presented here, were initially included in a study on HPV⁺ HNSCC patients followed by cfHPV-DNA in plasma at diagnosis/therapy, and follow-ups at Karolinska Institutet and Karolinska University Hospital, approved by the Swedish Ethical Review Authority (permission 2023-04595-01). Informed written consent was obtained from all patients in that study, including the two patients presented here.

METHODS

HPV in the tumors

HPV⁺ status in the primary tumors was defined as the cancer being HPV-DNA positive by PCR assay and overexpressing p16INK4a (p16⁺) in >70% of the cells [21,22], and data were obtained from patient records.

cfHPV-DNA in plasma

Plasma samples were collected at diagnosis, 3 weeks after initiation of radiotherapy and at regular follow ups after therapy. Collection and storage of the samples, extraction of cell-free DNA and evaluation of cfHPV-DNA by digital droplet PCR was followed as described previously [17,20].

CASE PRESENTATION

Case Report 1

The first case: was an almost 80-year-old male patient diagnosed with an HPV33 type positive TSCC T4N0M0, who, at the time of diagnosis, smoked 3-4 cigarettes per day, and used Swedish snuff tobacco but did not consume alcohol regularly.

Medical history: The patient had in the past a long history of alcohol and intravenous drug abuse. He was diagnosed with Hepatitis A, B and C in the 1970-ies, leading to liver cirrhosis and a hepatocellular cancer. In 2007 he received a liver transplant and has post-operatively developed a kidney failure (Chronic Kidney Disease Stage 3). The patient was immunosuppressed with mycophenolic acid as well as cyclosporin. Upon diagnosis he was also receiving per-oral treatment for hypertonia, hyperlipidemia, and diabetes mellitus type 2.

Treatment for TSCC: The patient was treated with chemoradiotherapy (CRT), Carboplatin (AUC2, Q1W) concluding 2 courses, but treatment was interrupted due to acute renal failure resulting in insufficient renal function. The patient could, however, obtain full dose radiotherapy (RT) up to 68 Gy, delivered in 2 Gy fractions which was completed around 2 months after his initial diagnosis. Shortly after completing the treatment, he was hospitalized due to headache and double vision. A computed tomography (CT) scan of the brain was performed, showing a local tumor progression with excessive growth into the base of the scull as well as the nasal cavity. The patient did not respond at all to the given cancer treatment and passed away one month later due to rapid disease progression.

cfHPV-DNA data: The patient had 3300 copies of HPV in the diagnostic sample and at 3-4 weeks after initiation of RT an increase was noted to 75000 copies, which correlated to the fact that the patient had a continuous a disease progression.

Case Report 2

The second case: was a male patient in his early 60-ies, who presented with an HPV16 positive BOTSCC T3N1M0. The patient was not a smoker at diagnosis.

Medical history: The patient had several comorbidities including Bence Jones myeloma (leading to kidney failure), hypertonia, and diabetes mellitus. He presented a myocadiac infarction at the age of 29 years and underwent a kidney transplantation in 2014 due to renal and heart failure. Two and a half years before being diagnosed with a BOTSCC the patient had undergone a percutaneous coronary intervention due to another cardiac event. The patient was treated with tacrolimus, everolimus and prednisolone for his renal transplant and bortezomib for his Bence Jones myeloma.

Treatment: The patient was treated with CRT with docetaxel as a radiosensitizer due to his impaired kidney function. He received three treatment courses of docetaxel (Q1W) which led to an increase in creatinine and additional chemotherapy was omitted. He was hospitalized during most of his treatment, initially for a peripherally inserted central catheter line infection, and subsequentially a staphylococcus aureus bacteremia.

The patient could complete radiotherapy (68Gy one month after his diagnosis). His condition was stable for

4 days after completed RT, when the patient presented with a fever and became confused. The patient received antibiotics due to a suspected aspiration pneumonia. During the period of confusion, the patient removed his nasogastric feeding tube several times. A bleeding occurred that was not possible to stop, and mucous from the infection could not be retracted. The patient died the same night. However, no evidence of disease progression could be confirmed.

cfHPV-DNA: the patient's diagnostic sample had 102.6 HPV copies, but no follow-up samples were available that could be evaluated.

DISCUSSION

Here, two case reports, one liver transplanted patient with an HPV33 positive TSCC T4N0M0 and one kidney transplanted patient with an HPV16 positive BOTSCC T3N1M0 are presented.

We noted that both patients were cfHPV-DNA positive at diagnosis, and the liver transplant patient with an HPV33 positive T4 TSCC had a higher cfHPV-DNA value than the kidney transplant patient with an HPV16 positive T3 BOTSCC. Furthermore, the former patient continuously presented increasing cfHPV-DNA values during and after treatment as his tumor progressed, while only one plasma sample of the latter patient could be analyzed. Unfortunately, both patients died shortly after completing therapy, one with progressive disease and the other of complications due to the treatment.

This report has limitations since it only includes two case reports. However, it suggests that although cfHPV-DNA can be monitored, organ transplant patients are so heavily treated with immunosuppressive drugs prior to their cancer therapy, that the latter still presents additional risks and side effects.

We suggest that these previously immunosuppressed patients post organ transplantation may need to be handled with extra caution and differently from non-organ transplanted patients. Special caution should be given when considering the use of chemotherapy. Evaluating the treatment efficacy of single treatment modalities, e.g. RT by monitoring cfHPV-DNA could be helpful when considering omitting chemotherapy. Moreover, it also likely, organ transplant patients should be checked regularly for the presence of HPV^+ OPSCC.

Nevertheless, these case reports emphasize the importance of conducting more studies of solid organ transplant patients presenting HPV^+ OPSCC.

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