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Case Report

ANAL CANCER IN A RENAL TRANSPLANT RECIPIENT: A CASE REPORT AND LITERATURE REVIEW

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SUMMARY – Anal carcinoma is a rare tumor in the general population accounting for 1%-2% of all malignancies. Most anal cancers are squamous cell carcinomas. Human papillomavirus and immunosuppression are the main risk factors for developing anal squamous cell carcinoma. Therefore, the incidence rate of anal squamous cell carcinoma is significantly higher in renal transplant recipients than in the general population. We present a patient who developed anal cancer nine years after renal transplantation. Since there was a significant diagnostic delay in our patient, we would like to emphasize the importance of regular screening for anal cancer in renal transplant recipients.

Key words: *Anal cancer; Renal transplant recipient; Immunosuppression; Human papillomavirus*

Introduction

Anal cancer is a rare malignancy with an incidence of 1-2/100,000 *per* year in the general population. It mainly occurs at the age of 60-65, affecting more often women than men[1,2]. An increased incidence rate has been detected in the highly developed countries over the past decade; for instance, the incidence rate in the USA has risen by 50% in the female population and 90% in the male population when comparing the data from 2017 with the data from 1992 to 2001[3]. The major risk factors for the development of anal squamous cell carcinoma (ASCC) include immunosuppression (caused by either HIV infection or immunosuppressive drugs), human papillomavirus (HPV) infection, anal receptive intercourse, and smoking[1].

Here we present a case of a renal transplant recipient (RTR) with anal carcinoma and genital warts, which were diagnosed with a significant delay.

Case Report

A 35-year-old male with end-stage renal disease due to immunoglobulin A nephropathy received a renal allograft from a deceased donor in September 2011, after four years of hemodialysis. Treatment of his primary kidney disease included cyclophosphamide and prednisone. The posttransplant immunosuppressive protocol included basiliximab induction followed by cyclosporine, mycophenolic acid, and prednisone maintenance. In December 2020, a tumorous formation in the perianal region was noticed and was initially misdiagnosed as hemorrhoids (Fig. 1). Since the tumor was growing, biopsy was performed in February 2021, and histopathologic analysis revealed a high-

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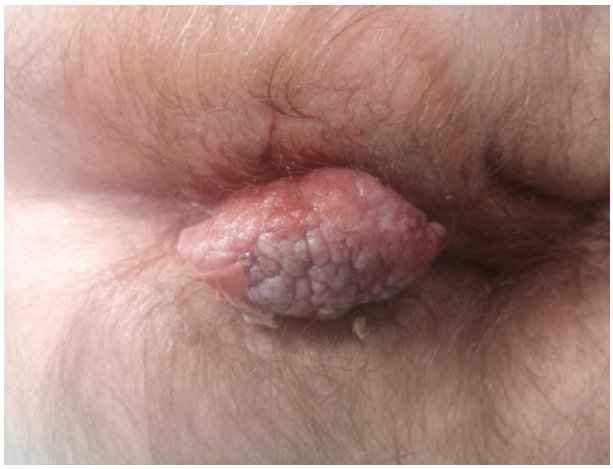

Fig. 1. Large verrucous tumor in the patient's anal and perianal area.

grade squamous intraepithelial lesion. The multi-slice computed tomography scan, which was done in March 2021, showed a sharply delimited expansive formation inseparably adhering to the anus with axial dimensions of 4.4x3.4 cm. No expansive formations were noticed in the colon. The patient underwent surgery in March 2021. The postsurgical histopathologic analysis verified well-differentiated, HPV positive squamous cell carcinoma 60x35x35 mm in size with the base diameter of 30 mm (pT3, G1) (Fig. 2). The tumor did not affect surgical margins, but marginal anal intraepithelial neoplasia (AIN) grade III was found. Immunohistochemically, tumor cells were positive for p16 (Fig. 3). Antibiotic therapy, which included ciprofloxacin and metronidazole, was administered postoperatively, and the doses were modified according to the renal function. Postsurgically, radiotherapy was recommended.

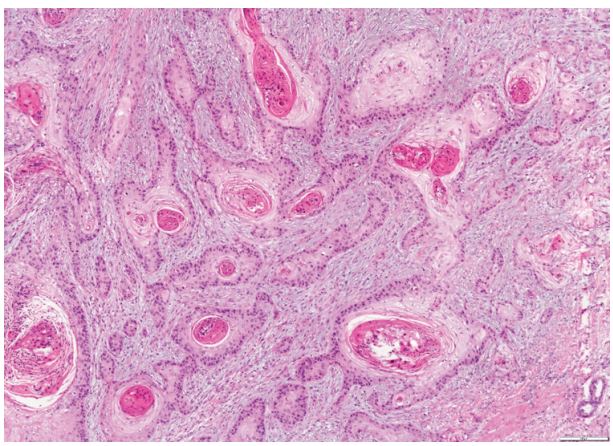

Fig. 2. Anal squamous cell carcinoma composed of large clusters of well-differentiated atypical squamous epithelial cells with large focal areas of keratinization (HE, X5).

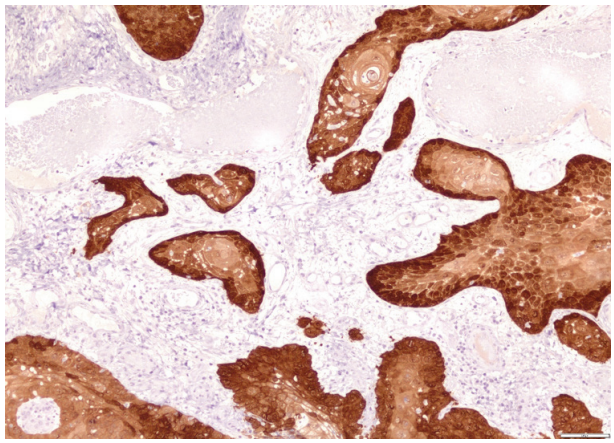

Fig. 3. Positive p16 immunostaining of tumor cells indicating human papillomavirus infection.

During dermatologic follow-up, numerous flat warts were present on the forehead, and there were also numerous confluent condylomata acuminata in the genital region. The patient indicated that these had been present from the beginning of immunosuppressive therapy. Topical imiquimod twice a week was prescribed for the treatment of genital condylomata. The patient was suggested to have a dermatoscopy check-up every six months regularly.

Discussion

Squamous cell carcinoma is the most prevalent type of anal cancer, accounting for 80% of all anal cancers. Although being rare cancer in the general population, ASCC is a significant burden in the specific population groups at an increased risk, including organ transplant recipients, HIV positive patients, and men having sex with men[4].

Recent studies have noticed that the risk of developing ASCC among solid organ transplant recipients is six times higher in comparison to the general population in the USA, Australia, New Zealand and Sweden[5,6]. Furthermore, a 14 times greater risk has been registered among the solid organ transplant recipients in Denmark[7]. When it comes to RTRs, the results of a large study in The Netherlands that included 1023 patients showed that the risk of developing ASCC was

122 times greater among RTRs compared to the general population[8]. Additionally, in solid organ transplant recipients, ASCC occurs at an earlier age than in the general population[9]. Immunosuppression is associated with worse prognosis of ASCC because immunosuppressed patients have higher rates of disease progression and recurrence[10]. There is little evidence regarding the association between particular immunosuppressants and ASCC. Some authors encourage replacement of calcineurin inhibitors by mammalian target of rapamycin (mTOR) such as sirolimus in organ transplant recipients who have developed malignancy[11].

Persistent HPV infection is the most significant factor in the pathogenesis of ASCC. Up to 88% of ASCC are associated with HPV infection, particularly the 16 and 18 genotypes[1]. A Danish and Swedish study revealed that 90% of female patients and 64% of male patients with anal cancer tested positive for HPV[12]. An American study found that 87.9% of patients with anal cancer had HPV[13]. Moreover, it has been estimated that persistent HPV infection in RTRs doubles the risk of HPV-induced cancers[5]. HPV infection is associated with AIN as well. The oncogenic subtype 16 has been associated with AIN in most cases. AIN is classified into three grades; grade 2 and grade 3 are precursors of anal cancer[14].

Human papillomavirus has the ability to integrate its genome into the genome of the human cell. Moreover, HPV expresses oncogenes E6 and E7 which cause promotion of tumor proliferation and transformation of normal cells into malignant cells by inhibiting the activity of the retinoblastoma protein (pRb) and p53. These two proteins are crucial for the regulation of cell proliferation[15]. Inactivation of pRb leads to upregulation of p16, a cyclin-dependent kinase inhibitor essential in regulating the cell cycle. Overexpression of p16 is considered as a surrogate marker of HPV infection[16].

Brown *et al.* report a significantly higher rate of oncogenic HPV subtypes 16 and/or 18 among female RTRs compared with the immunocompetent group[17]. It is considered that immunosuppression has a crucial role in facilitating persistent HPV infection, which is necessary for the occurrence of AIN and its progression to ASCC[18]. Furthermore, persistent HPV infection in RTRs increases the risk of ASCC approximately 100-fold[19].

On the other hand, it has been noticed that HPV infection might positively impact the patient outcome since it increases the disease-specific survival and overall survival[1]. Also, p16 has a similar effect because it increases the disease-specific survival by 55% and overall survival by 46%[1]. In addition, HPV positive AIDS responds better to chemoradiotherapy[15].

Our patient was a renal transplant recipient who developed HPV positive and p16 positive ASCC. Unfortunately, anal cancer was misdiagnosed as hemorrhoids despite the above mentioned, well-established data on a significantly higher incidence of AIN and ASCC in RTRs. Diagnostic delay in ASCC is not uncommon. A recent study suggests that the mean time elapsed from the appearance of symptoms to diagnosis was 7.4 months, and from referral to a primary care provider 3.2 months. This long time between the appearance of symptoms and diagnosis of the disease is usually due to resemblance of the ASCC symptoms to the symptoms of other diseases of the anorectal area that are commonly benign. The same authors report that 27% of initial diagnoses of ASCC were misdiagnoses of hemorrhoids, similarly to our patient[20].

It should be emphasized that our patient also had genital warts that should have been recognized as another risk factor for the development of ASCC. Even though genital warts are etiologically associated with non-oncogenic HPV-6 and HPV-11, their association with ASCC in the general population can be explained by the fact that patients with both genital warts and ASCC are more likely to engage in high-risk sexual behavior[21]. In RTRs, external anogenital warts may suggest the presence of internal HPV-induced lesions. Additionally, due to immunosuppressive treatment, preneoplastic lesions may resemble benign anogenital warts[22].

The presented patient confirms the necessity of ASCC screening in RTRs. According to Ching-Hong, the screening should include anal Pap test as the first step, followed by high-resolution anoscopy in the case of normal anal cytology and biopsy for histologic analysis of suspicious lesions if anoscopy findings are abnormal[9].

Since the vast majority of ASCC diagnoses are associated with HPV infection, prophylactic HPV vaccines could be beneficial for preventing AIN and ASCC. However, there is a reluctance regarding vaccination against HPV in RTRs due to insufficient data regarding the safety and efficacy of these vaccines in RTRs[23]. Furthermore, it is desirable to administer the HPV vaccines in eligible patients before transplantation to provoke a significant antibody response[9].

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Sažetak

KARCINOM ANUSA U BOLESNIKA S TRANSPLANTIRANIM BUBREGOM: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Karcinom anusa, koji čini 1%-2% svih malignih bolesti, rijedak je tumor u općoj populaciji. Planocelularni karcinom je najčešći tip karcinoma anusa. Humani papilomavirus i imunosupresija glavni su čimbenici rizika za razvoj analnog planocelularnog karcinoma. Stoga je stopa incidencije analnog planocelularnog karcinoma značajno veća u bolesnika s transplantiranim bubregom nego u općoj populaciji. Prikazujemo bolesnika s transplantiranim bubregom koji je razvio analni karcinom devet godina nakon transplantacije. S obzirom na to da je u našeg bolesnika došlo do značajnog kašnjenja u postavljanju dijagnoze, htjeli bismo naglasiti važnost redovitog probira na karcinom anusa u bolesnika s transplantiranim bubregom.

Ključne riječi: *Karcinom anusa; Primatelj bubrežnog presatka; Imunosupresija; Humani papilomavirus*