Case Report

Oral carcinoma in two young recipients of stem cell transplant

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ABSTRACT

Patients with stem cell transplantation have an increased risk of developing new malignancies. Oral squamous cell carcinoma is rare after stem cell transplantation. We herein report two cases of oral squamous cell carcinoma developing in young patients after stem cell transplantation.

Key words: Squamous cell carcinoma, stem cell transplantation

INTRODUCTION

Patients who receive stem cell transplantation are known to have an increased risk of developing new malignancies. Bhatia *et al*. reported an increased risk of developing malignancies after bone marrow transplantation with an estimated actuarial incidence of 5.6% ± 2.2%.[1] Compared to the general population, there was an 11-fold increase in the risk of malignancy in patients who underwent bone marrow transplant for various reasons at the University of Minnesota. The posttransplant tumors included hematological and solid tumors. We report two patients who developed oral malignancies soon after receiving stem cell transplant for a nonmalignant condition.

CASE REPORTS

Case 1

In January 2008, a 36-year-old male patient presented with painful ulcer on the right side of mouth and difficulty in chewing for about 6 weeks duration. He gave history of tobacco abuse (oral tobacco and cigarettes) for 20 years and daily alcohol consumption. The patient also had a history of road accident leading to facial palsy, 5 months back for which he received stem cell transplantation. No further detail of stem cell transplantation was available from his records. On examination in January 2008, he was found to have a 4 × 3 cm ulcer on the right buccal mucosa starting 2.5 cm away from the oral commissure extending inferiorly to the gingivo-buccal sulcus and posteriorly to the retromolar trigone. Histological examination of this lesion showed a tumor arranged in sheets. The tumor cells are moderately pleomorhic, round to polygonal in shape with vesicular nuclei, prominent nucleoli, and moderate amount of eosinophilic cytoplasm, confirming the diagnosis of squamous cell carcinoma [Figure 1a]. Frequent mitosis was also noted. Neck nodes were not palpable and there was no evidence of distant metastasis. He was diagnosed to have stage II squamous cell carcinoma of buccal mucosa

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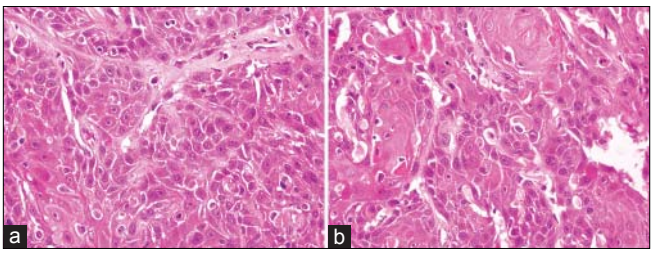

Figure 1: Squamous cell carcinoma (Hematoxyline and Eosin stain ×400): (a) Case 1. Histological section show sheets of pleomorphic tumor cells with individual cell keratinisation. (b) Case 2. Histological section show nests of tumor cells with individual cell keratinization and keratin pearls formation

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and underwent wide local excision of tumor with split-skin graft and right side neck node dissection followed by external radiation 60 Gy/6 weeks/30#. He was found to be disease free 6 weeks after completion of treatment and is on regular follow-up since then.

Case 2

A 37-year-old farmer complained of a nodular swelling in the right lower jaw, first noticed in April 2009. The swelling was initially painless but was progressively increasing in size and extending to adjacent floor of mouth and tongue. Within a period of 6 weeks, the mass became painful and ulcerated. When he presented to the Radiotherapy OPD, he had difficulty in eating and speaking because of a fixed tongue and was in severe pain. He denied any history of tobacco or alcohol abuse. On examination of the oral cavity, he had a big, hard mass involving the right lower alveolus, the floor of mouth and the tongue from 1 cm behind the tip to the posterior third of tongue. Ankyloglossia was present and there was a 2 × 2 cm ulcer over the right floor of mouth and adjacent ventral surface of the tongue. No neck node was palpable; however, there was a discrete, hard mobile swelling at the left upper arm. His previous discharge cards revealed that he had been diagnosed with carcinoma penis in 2007 for which he underwent partial penectomy followed by inguinal lymph nodes dissection and three courses of chemotherapy. In December 2008, he was diagnosed to have peripheral vascular disease for which he received stem cell transplant under sciatic block and now he presented with an oral lesion. Histological examination of the oral lesion showed a tumor arranged in nests with keratin pearl formation. The tumor cells are mildly pleomorphic, having vesicular nuclei and moderate amount of amphophilic cytoplasm, confirming the diagnosis of well-differentiated squamous cell carcinoma [Figure 1b]. FNAC from the nodule in the arm was reported as metastatic squamous cell carcinoma. Chest X-Ray showed a well-defined cavitary lesion in the right upper zone of the lung, possibly metastasis and ultrasound examination of the abdomen and pelvis showed a 3 × 3 cm space occupying lesion in liver which was suggestive of metastasis. In view of his advanced disease and poor nutritional status, he was found suitable for palliative radiotherapy. He showed partial subjective response to treatment but succumbed to his illness after a week.

DISCUSSION

Posttransplant solid tumors have been reported after hematological stem cell transplant.[1-3] Curtis *et al*. found elevated risk of developing malignant melanoma and tumors of oral cavity, brain, thyroid, liver, and bone in recipients of bone marrow transplantation.[2] In a review article, Deeg and Socie subdivided the posttransplant malignancies into three major categories namely PTLD and lymphomas, hematologic and solid tumors.[3] One of the initial large series was from Seattle which reported solid tumors in recipients of allogenic stem cell transplantation.[4] These tumors included glioblastoma, melanoma, squamous cell carcinoma, adenocarcinoma, hepatoma, and basal cell carcinoma. Total body irradiation was considered to be a risk factor for developing posttransplant malignancies. Solid tumors have also been reported in patients who received autologous stem cell transplant. Andre *et al*. compared patients of Hodgkin's lymphoma treated with high dose chemotherapy and autologous stem cell transplant with matched patients treated conventionally.[5] They found that the risk factors for a second malignancy was >40 years of age and use of peripheral stem cells. Solid tumors were more frequently seen in grafted patients compared to ungrafted ones (RR 5.19, $P = 0.001$).

An increased risk of developing solid tumors after stem cell transplant, specifically melanoma, brain, and oral cavity tumors, was observed by Scott Baker *et al*. in their study in 3372 recipients of stem cell transplantation over a period of 27 years. This study reported a standardized incidence ratio 2.8 for solid tumors.[6] The excess risk of developing any posttransplant malignancy in this group of patients was 102.7 cases/10,000 persons/year adjusting for age and sex. The technology of stem cell transplant was introduced in our part of the country only recently and it is interesting to note that we found two cases of oral carcinoma within a span of 15 months. The first patient was habituated to tobacco and alcohol but the second patient denied such abuse.

The risk of developing a malignancy after stem cell transplant increases with time. The cumulative incidence of any solid tumor after bone marrow transplant is 2.2% at 10 years and 6.7% at 15 years.[2] At 20 years, cumulative index for any posttransplant malignancy was 6.9% and the same for solid tumors was 3.8%.[6] It is important to note that the cumulative incidence for solid tumors did not plateau even after 20 years indicating a probability of further increase.[6,7] Our both patients developed a new malignancy in the oral cavity within months of receiving stem cell transplant. Witherspoon *et al*. reported solid tumors, 2.5 months after allogenic transplant and another series reported second malignancy as early as 1.5 months after marrow or blood stem cell transplant.[4,8]

Prolonged use of drugs like Azathioprine, Cyclosporine and steroids is known to be a major cause of posttransplant squamous cell carcinoma.[9] Severe chronic GVHD and prolonged therapy with these immunosupressives are significant risk factors for squamous cell carcinoma of skin and oral cavity. Total body irradiation was found to be a risk factor with higher doses corresponding to higher risks.[2] Our patients were not on any immunosuppressive agent when they reported for treatment of oral cancers. However, it would be advisable to conduct clinical screening for

squamous cell carcinoma in all patients on prolonged immunosupression.[9]

Age of the recipient at the time of stem cell transplant is also considered to be a risk factor for developing malignancies.[2,5,7] While one study reported age <10 years at the time of transplant a risk factor for solid tumors, multivariate analysis in other studies reported age ≥35 years as a risk factor for posttransplant solid tumors.[2,5,7,8,10] The two patients in this report were young, less than 40 years of age. The mean age of patients with head and neck cancer at our center is 61 years with only about 10% patients aged less than 40 years (unpublished data).

The two cases reported here are young compared to the mean age of head and neck cancers as a group. Both had received stem cell transplantation months before being diagnosed with squamous cell carcinoma of oral cavity. The second patient did not give history of tobacco or alcohol abuse but did have a penile cancer to begin with. According to SEER cancer registry, there is a borderline significant increase in overall subsequent primary cancer risk among men surviving at least 2 months following a diagnosis of penile cancer. The cumulative incidence of developing a second cancer in these patients is 19.7% at 20 years (95% CI = 17.5-22.1%). The excess risk of subsequent cancer was most pronounced for cancer of buccal cavity and respiratory tract.[11] Smoking, alcohol and HPV probably played a role in developing these tumors. Though it is not possible to establish any cause–effect relationship, the purpose of reporting these patients is to draw attention to the association of stem cell transplantation and posttransplant malignancy. As suggested by some authors, these patients should be regularly screened for common posttransplant malignancies. Since the cumulative risk for solid tumors do not plateau even after 20 years, the follow-up in these patients must be meticulous and lifelong.

CONCLUSIONS

Young patients after stem cell transplantation are at increased risk of developing new cancers. These patients should be under regular vigil for common posttransplant malignancies so that earlier detection and treatment is possible.

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