Squamous Cell Carcinoma of the Oral Tongue in Two Patients Previously Exposed to Long-Term Pegylated Liposomal Doxorubicin

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Pegylated liposomal doxorubicin (PLD) as single agent is being used in different clinical scenarios, including treatment of recurrent epithelial ovarian cancer, HIV-related Kaposi's sarcoma, and desmoid tumors. Prolonged administration has shown a good safety profile [1–3]. Recently, concerns of a higher risk for oral cavity squamous cell carcinoma in patients with a history of prolonged exposure to PLD was reported [4, 5]. We present two cases of oral tongue cancer in patients who never smoked or drank previously but were exposed to PLD.

The first case is a 35-year-old man with a history of familial adenomatous polyposis/Gardner's syndrome who underwent total colectomy with ileoanal anastomosis for polyposis in 1999. In January, 2004, the patient complained of abdominal distension. An abdominal computed tomography scan showed a 14-cm mesenteric mass. The biopsy was consistent with desmoid tumor. The patient started PLD at a dose of 40 mg/m² every 4 weeks. Treatment was continued until August, 2006, with continued tumor control. In March 2011, the patient underwent hemiglossectomy with neck dissection. Pathology demonstrated a tumor–node–metastasis (TNM) stage T1N2bM0, poorly differentiated squamous cell carcinoma. In situ hybridization for human papilloma virus (HPV)-16/18 was negative. The patient received concomitant postoperative chemotherapy plus radiation.

The second case is a 47-year-old man with a history of HIV/AIDS and disseminated Kaposi's sarcoma diagnosed in 2002. He started antiretroviral therapy and PLD at a dose of 20

mg/m² every 4–8 weeks until he attained a complete remission in June of 2005. In March, 2011, he had near-total glossectomy and left-sided selective neck dissection for a stage T3N2bM0, moderately differentiated, squamous cell carcinoma. In situ hybridization for HPV-16/18 was negative. The patient received postoperative radiotherapy.

Carcinomas of the oral cavity are very uncommon in younger patients in the absence of alcohol or tobacco exposure [6, 7]. There is a higher incidence of extracolonic malignancies in patients with Gardner's syndrome but no data linking this entity with squamous cell carcinomas of the oral cavity [8]. Even though there has been an increasing incidence of non-AIDS-defining malignancies in the post–highly active antiretroviral therapy era, the incidence of cancers of the oral cavity in HIV patients is <1% [9]. Treatment of HIV-related Kaposi's sarcoma with PLD has been associated with squamous cell carcinoma of the tongue [2]. It was reported that three of 16 patients with ovarian cancer who were exposed to long-term PLD for a period ≥3 years developed oral cavity malignancies and one patient developed sublingual mucosal high-grade dysplasia [4, 5]. All the lesions were HPV-16/18 negative. Considering that none of our patients were exposed to the risk factors for oral cavity malignancies but were exposed to long-term PLD, our observation, in addition to those cases previously reported [4, 5], supports the hypothesis that long-term exposure to PLD is possibly associated with the development of squamous malignancies of the oral cavity. This long-term toxicity might be explained by the fact that PLD selectively

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accumulates in the mucosa of the head and neck area [10]. Serial oral cavity examination and a level of suspicion for patients who have received extended courses of PLD appear warranted.

AUTHOR CONTRIBUTIONS

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EDITOR'S NOTE: We publish in this issue a brief series of related papers and letters that examine possible side effects of long-term exposure to pegylated liposomal doxorubicin (PLD). See pages 1534–1540 for a report of the occurrence of the renal thrombotic microangiopathy in ovarian cancer patients exposed to PLD; pages 1541–1546 for a report of squamous cell carcinoma (SCC) of the mouth in non-smoking women with recurrent ovarian cancer; and pages 1596–1599 for two additional Letters to the Editor that relate other cases of SCC of the oral cavity in patients with long-term PLD exposure.