


A case of tongue cancer manifesting from oral leukoplakia after long-term administration of pegylated liposomal doxorubicin

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Abstract

We present a case of tongue cancer manifestation from oral leukoplakia after administration of pegylated liposomal doxorubicin (PLD). A 56-year-old woman was diagnosed with ovarian cancer. After preoperative chemotherapy with paclitaxel and carboplatin (TC), she underwent interval debulking surgery. Five cycles of TC therapy were carried out as adjuvant chemotherapy; however, recurrence was observed. Despite administration of gemcitabine-carboplatin therapy, the patient's condition was judged as advancing to a progressive disease. PLD treatment was completed at a total dose of 1140 mg/m². Two months after the end of treatment, the patient was diagnosed with leukoplakia. The leukoplakia lesion became thicker at each 3-month follow-up. She was diagnosed with tongue cancer and underwent a partial resection 2 years and 3 months after the completion of PLD treatment. Our report suggests that the risk of malignant transformation to tongue cancer persists even after the completion of treatment with PLD.

INTRODUCTION

Leukoplakia is an oral, potentially malignant disease which presents as a white lesion that does not peel off with friction. It is often found on the oral mucosa, especially in the buccal mucosa and tongue. Clinically, it is described as 'a markedly white lesion of the oral mucosa that cannot be characterized as any other disease'. Differential diagnosis of leukoplakia include fungal infection, frictional keratosis (caused by something such as ill-fitting dentures and repeated biting of the cheek) and lichen planus. Leukoplakia cannot be rubbed off the oral mucosa, distinguishing it from other cause of white lesions such as oral candidiasis. Generally, frictional keratosis will be adjacent to ill-fitting denture or sharp teeth and will soon disappear if the causative factor is removed. Histopathologically, leukoplakia includes a range of conditions ranging from epithelial hyperkeratosis to epithelial atypia and can include intraepithelial and invasive carcinomas. However, lesions diagnosed as intraepithelial carcinoma or invasive carcinoma are not considered as leukoplakia. The key predictors of oral cancer are heterogeneous and widespread lesions, lesions

on the lateral margin of the tongue or floor of the oral cavity and lesions with histological dysplasia. It is estimated that 1–36% of patients affected by leukoplakia will develop oral cancer [1]. Mathematically, the estimations in studies using epidemiological data suggest that the rate at which leukoplakia develops into oral cancer is <1% per year [2]. Furthermore, smoking, alcohol consumption and human papilloma virus infections are known risk factors of leukoplakia [3]. However, molecular markers that predict malignant transformations in oral cancer are not known [4].

Pegylated liposomal doxorubicin (PLD) is an anticancer drug used in the treatment of certain recurrent cancers, including ovarian cancer. There have been some reports of an increase in the incidence of oral cancer in patients administered increasing PLD doses [5–9]. However, cases of tongue cancer manifesting from oral leukoplakia after long-term administration of PLD have not been reported.

In this article, we report a patient with recurrent ovarian cancer treated with PLD who developed leukoplakia after 2 months and tongue cancer at 2 years and 3 months after completion of PLD treatment.

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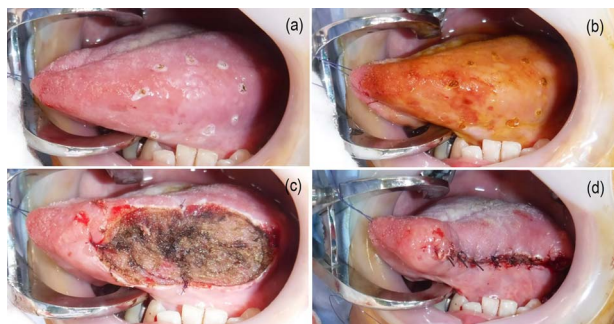


Figure 1. Intraoperative images; (a) set a 10-mm surgical margin around the tumor before resection; (b) confirm unstained area with Lugol's solution; (c) cut the deep part in a wedge shape; the resection margin is negative for cancer; (d) suture in a straight line.

CASE REPORT

A 56-year-old woman with a past medical history of pulmonary *Mycobacterium avium* complex and hypertension visited our hospital with the chief complaint of abdominal mass. Computed tomography and magnetic resonance imaging revealed malignant ovarian tumors with severe ascites and peritoneal dissemination. She was a non-smoker and non-drinker. Exploratory laparoscopic surgery and biopsy of the peritoneal dissemination were performed. The pathological diagnosis was high-grade serous carcinoma of the ovary. After three cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin (TC), she underwent an interval debulking surgery (hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, lower anterior resection and diaphragmatic resection). Five cycles of TC therapy were administered as adjuvant chemotherapy. Approximately, 10 months after the completion of TC therapy, recurrence was observed in the paraaortic lymph nodes. Gemcitabine-carboplatin therapy was subsequently administered; however, the patient's condition was judged to be a progressive disease and PLD was administered thereafter. A higher incidence of oral ulcer has been reported after PLD administration [5–9]. At our hospital, all patients undergo a dental examination before each PLD administration to check for oral ulcer. We also provide regular follow-up at the Oral Surgery Department during PLD administration.

PLD was administered for 22 months and treatment was completed at a total dose of 1140 mg/m² in partial response to PLD. Two months after the end of treatment, a white lesion was found on the left side of the tongue. The white lesion was not rubbed off the oral mucosa. She does not have all any of the reported risk factors of leukoplakia and tongue cancer (smoking history, drinking history, chronic cheek biting, ill-fitting dentures, sharp teeth, syphilitic glossitis and candida infection). Therefore, it was diagnosed as leukoplakia and was considered that leukoplakia developed due to PLD administration. The leukoplakia became thicker at each 3-month follow-up and a biopsy revealed squamous cell carcinoma. She was diagnosed with tongue cancer and underwent a partial resection at 2 years and 3 months after completion of PLD treatment (Fig. 1). The histopathological diagnosis was squamous cell carcinoma of the tongue, pT1aNxM0 (Fig. 2). The patient showed no recurrence 10 months after the surgery.

Patient's informed consent to publish this case report was obtained.

DISCUSSION

Oral cancer develops after a certain period of leukoplakia. Previously, 11 cases of oral cancer after PLD administration have been reported (Table 1) [5–9]. In all cases, oral cancer was diagnosed after the onset of symptoms such as discomfort or pain in the oral cavity. In these cases, it is unclear whether oral cancer developed after leukoplakia or in its absence. To our knowledge, there are no other reports of tongue cancer manifesting from oral leukoplakia after administration of PLD.

In this case, the patient developed leukoplakia at 2 months after the end of PLD treatment. The cumulative PLD dose was 1140 mg/m². This case does not indicate a particularly early finding of leukoplakia; it does not involve a particularly early discovery as compared to other previous reports (Table 1).

Leukoplakia can develop into oral cancer even after the discontinuation of PLD administration. According to a pharmacokinetic study, PLD confers higher plasma concentrations because of its small volume of distribution than non-liposomal doxorubicin [5]. Liposomes

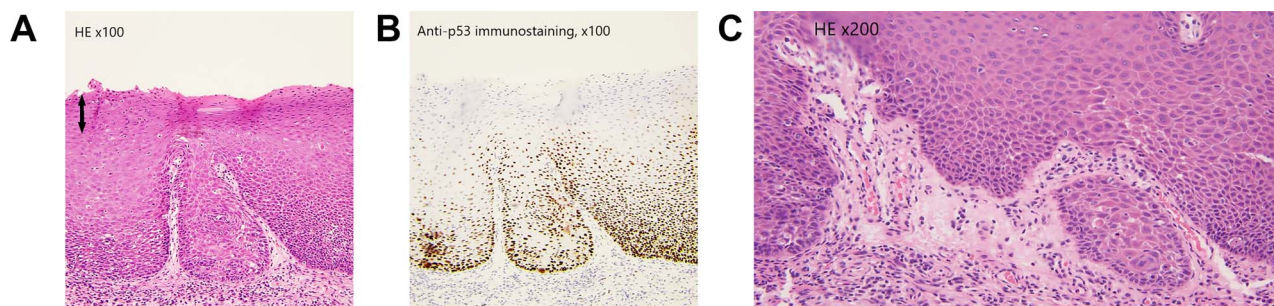


Figure 2. Histopathological images; (A) thick, well-defined complex keratinization is identified in the superficial layer (black arrow); (B) the atypical cells were confined to one-half to one-third of the basal layer; these cells were markedly atypical; (C) loss of basal cell polarity, cellular and nuclear polymorphism, large nucleoli and single or groups of cells in the spinous and basal layers are present.

Table 1. Oral cancer PLD treatment. (a) PLD. (b) TC; paclitaxel and carboplatin

Reference	Age/sex	First cancer diagnosis	Treatment	Duration of PLD use at time of diagnosis (months)	PLD cumulative (mg)	SCC site/TN stage	Treatment
Cannon et al. [5]	76/F	Tubal cancer	Cisplatin and PLD, then i.p. cisplatin and floxuridine, then PLD maintenance	96	1800	Tongue, T1N0	Glossectomy and radiation therapy
	67/F	Ovarian cancer	Carboplatin and paclitaxel, then topotecan and PLD, then PLD maintenance	132	2320	Sublingual dysplasia	Sublingual dysplasia managed with resection
	52/F	Ovarian cancer	Carboplatin, paclitaxel and cyclophosphamide, then hyperthermic i.p. paclitaxel and mitomycin C, then PLD and carboplatin, then PLD maintenance	80	3000	Multiple oral SCC, T1N0	Multifocal oral SCC: 3 separate T1N0 lesions (left retromolar, anterior hard palate and right buccal mucosa); treatment: 1 resection of each lesion and neck dissection followed by radiation
	71/F	Ovarian cancer	Carboplatin and paclitaxel with i.p. cisplatin, then carboplatin and PLD, then PLD maintenance	32	2116	Tongue, T1N0	T2N0 SCC of the tongue treated with partial glossectomy
	54/F	Ovarian cancer	Carboplatin and paclitaxel with i.p. cisplatin and topotecan, then carboplatin and PLD, then PLD maintenance, then velaparib and cyclophosphamide	30	1696	Gingiva	T1N0 below second molar gingival: wide excision
Ben-David et al. [6]	66/F	Ovarian cancer	Surgery → PLD	84	?	Maxilla, Stage III	Wide right subtotal maxillectomy
	63/F	Kaposi's sarcoma	PLD	48	?	Maxilla, Stage I	Wide left subtotal maxillectomy
Bonomi et al. [7]	35/M	Desmoid tumor	PLD 40 mg/m ² q4w × 2 yr	60	960/m ²	Tongue, T1N2bM0	Hemiglossectomy with neck dissection → CCRT
	47/M	Pulmonary Kaposi's sarcoma	PLD 20 mg/m ² 4–8wk 3 yr	72	>720/m ²	Tongue, T3N2bM0	Near-total glossectomy and left-sided selective neck dissection → radiotherapy
Matsuo et al. [8]	57/F	Uterine papillary serous carcinoma	TC → PLD	Shortly after	3924	Buccal, T4bN0	Radiotherapy → chemotherapy
Gu et al. [9]	28/F	Giant cell bone tumor	PLD → denosumab	36	1260	Tongue, T1N0M0	Partial glossectomy and left supraomohyoid neck dissection

that release doxorubicin and its metabolites accumulate, especially in the skin and mucous membranes. Long-term exposure to doxorubicin is suspected to be the cause of secondary oral malignancies.

Previously, we have reported that the incidence of leukoplakia increases with increasing cumulative PLD doses [10]. This was a retrospective study of 114 patients previously treated with PLD in which total PLD dose was an independent risk factor. Receiver operating characteristic curve analysis showed that a total PLD dose of 400 mg/m² was the optimal cut-off value (sensitivity was 100% since the specificity was 88.8%). Therefore, 400 mg/m² is considered to be an index that requires attention. There were no cases of oral cancer at the time of this retrospective study.

Here, we report a case in which leukoplakia was diagnosed 2 months after the completion of PLD treatment and tongue cancer at 2 years and 3 months after the completion of PLD treatment (total dose of 1140 mg/m²). Since an increase in the total dose of PLD causes the development of leukoplakia, careful surveillance is required, especially when PLD is administered above a total dose of 400 mg/m². Leukoplakia may develop into oral cancer even if PLD administration is terminated. Therefore, consistent follow-up is required. In our case, the risk of development of tongue cancer was considered at the time of the diagnosis of leukoplakia. The patient was diagnosed with tongue cancer at an early stage.

In conclusion, our report suggests that oral cancer develops after the administration of PLD and after a certain period of leukoplakia and that the risk of malignant transformation to oral cancer continues even after completion of PLD treatment. Although oral cancer development after PLD administration has been reported previously, this is the first case of PLD-induced leukoplakia transformed to oral cancer during long-term monitoring. Continuous oral monitoring is necessary over the long term even after PLD treatment is completed and particularly for cases in which the total dose exceeds 400 mg/m².

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CONFLICT OF INTEREST STATEMENT

None declared.

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CONSENT

Written consent was obtained from the patient.

GUARANTOR

Dr Mai Nishimura.

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