CASE REPORT

Oral squamous cell carcinoma in a patient treated with long-term pegylated liposomal doxorubicin for recurrent ovarian cancer

Matteo Pezzoli, Maurizio Bona Galvagno, Guido Bongioannini

ENT Department, Mauriziano Hospital, Torino, Italy

Correspondence to
Dr Matteo Pezzoli,
ma.pezzoli@libero.it

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SUMMARY

We present a case of a woman who developed an oral squamous cell carcinoma (SCC) after being treated for a recurrent ovarian carcinoma with subtotal gastric resection and adjuvant pegylated liposomal doxorubicin (PLD). She received six cycles of PLD induction and maintenance therapy, which was continued for 5 years. She was free from disease at the following visits but 3 years later she developed SCC of her left inferior edentulous gums. The patient was negative for human papillomavirus and had never smoked in her life or had a history of alcohol use or any other environmental risk factors. PLD is known to accumulate in eccrine glands of the hands and the feet and in the oral mucosa, therefore causing skin toxicity and mucositis. It is conceivable that this specific biodistribution to the oral mucosa may be responsible for the onset of SCC.

BACKGROUND

The carcinogenic effects of chemotherapy are a well-known long-term side effect that may occur months or years after treatment. However, the causal effect is often difficult to demonstrate as other factors such as genetics, predisposition, immunodeficiency, environmental exposures or lifestyle can play a crucial role. Chemotherapy agents known to be carcinogenic are alkylating agents, topoisomerase II agents and anthracyclines.¹ Pegylated liposomal doxorubicin (PLD) is a liposomal encapsulated form of the chloride salt of doxorubicin. The initial approved indication for PLD was the treatment of Kaposi sarcoma in patients with human immunodeficiency syndrome. Its use for platinum-refractory ovarian cancer was approved in the USA in 1999 and in Europe in 2000. PLD gained popularity because it is the only non-platinum single agent that has shown a significant survival advantage in the second-line treatment of ovarian cancer in phase II and phase III trials.^{2 3}

PLD has good tolerability, as demonstrated in both prospective and retrospective studies.⁴ However, the side effects of PLD therapy include dermatological diseases (eg, palmar-plantar erythrodysesthesia) and, less commonly, stomatitis. The development of secondary malignancies, predominantly lymphomas, has also been reported in HIV-positive patients treated for Kaposi sarcoma.⁵ Recently, five cases of squamous cell carcinoma (SCC) of the oral cavity have been described in a case series of patients treated with long-term PLD

who were non-smokers and with no known risk factors for human papillomavirus (HPV).⁶ In this report we describe a further case of SCC in a woman with no other risk factors who was treated for more than 6 years with PLD for a recurrent ovarian cancer.

CASE PRESENTATION

A non-smoking and non-drinking woman aged 42 years was diagnosed with a stage IIIc ovarian carcinoma in September 2002. Her DNA tested positive for BRCA-1 mutation. She underwent a hysterectomy with bilateral annessiectomy and omentectomy and was treated postoperatively with six cycles of carboplatin-paclitaxel. In 2004 she had recurrent disease invading the epiploon and the retroperitoneum, so she underwent subtotal gastric resection. Postoperatively, she received six cycles of PLD induction and was then placed on maintenance therapy (32 mg/m² every 6 weeks), which was continued until 2010. She was free from disease at the following visits but in 2013 she noticed a white lesion on her left inferior edentulous gums (figure 1).

INVESTIGATIONS

A biopsy revealed high-grade dysplasia (figure 2); ultrasound examinations did not show any lymph node involvement. HPV expression was negative and the tumour lacked p16 expression.

DIFFERENTIAL DIAGNOSIS

The lesion clinically presented as a solitary white lesion. Differential diagnosis included benign conditions such as a contact or morsicatio lesion, a single lesion of lichen planus, a white sponge

Figure 1 The lesion in the oral cavity.

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Figure 2 Section of the biopsy specimen stained with H&E.

naevus, a potentially malignant lesion such as leucoplakia or a squamous cell cancer. Given the absence of any identifiable local cause, a definitive diagnosis was obtained by biopsy.

TREATMENT

She underwent complete excision of the lesion under general anaesthesia and the pathology showed moderately differentiated keratinising T1G2 SCC (figure 3), with 2 mm depth of invasion and disease-free margins. No lymphovascular invasion or perineural invasion was identified. No further radiotherapy was planned.

OUTCOME AND FOLLOW-UP

The patient is currently under regular follow-up and free from disease.

DISCUSSION

SCC of the oral cavity is a disease that occurs most frequently in men and is mainly caused by the use of tobacco and alcohol. HPV has been considered in oral carcinogenesis and, even if its role in cancer of this specific area is still uncertain, there are recent data suggesting that SCC occurring in patients with no other risk factors may be related to HPV infection with expression of p16 protein.⁷ In particular, as seen in oropharyngeal

Figure 3 Section of the surgical specimen stained with H&E.

cancer, HPV-positive tumours have a peak in younger patients and seem to have a worse prognosis.⁸

Our patient was HPV negative and had never smoked in her life or had a history of alcohol use or any other environmental risk factors. She tested positive for a BRCA-1 mutation; however, even if a relationship between such mutation and laryngeal cancer has been reported,⁹ there is no link between deleterious BRCA mutations and cancer of the oral cavity.

A previous report has shown that as many as 24% of head and neck cancers are found in patients over 70 years old¹⁰ and that the aetiology of cancer at this age is not related to HPV, alcohol or tobacco use,⁸ thus representing a distinct clinical subgroup. At the time of diagnosis our patient was aged 53 and without any risk factor for oral SCC.

A literature review revealed four previous reports on the administration of PLD and predisposition to oral cancer,^{6 11–13} with a total of nine cases described from 2012. All the patients were women and they did not have significant risk factors apart from exposure to PLD. Six patients were treated for recurrent ovarian carcinoma, one for metastatic bone giant cell tumour, one for Kaposi sarcoma and one for recurrent uterine papillary carcinoma.

PLD is currently approved for AIDS-related Kaposi sarcoma, platinum/paclitaxel-refractory ovarian carcinoma and metastatic breast cancer. Because of the low incidence of severe side effects,¹⁴ it is believed to be tolerable for long periods of time.¹⁵ Due to the encapsulation of the drug inside liposomes, it has a slow release and better accumulation in tissues with increased vascular permeability, a characteristic of tumours with neoangiogenesis.¹⁶ PLD also accumulates in eccrine glands of the hands and the feet⁶ and in the oral mucosa, therefore causing skin toxicity and mucositis. It is conceivable that this specific biodistribution to the oral mucosa may be responsible for the onset of SCC. Interestingly, cases of cancer of the conjunctiva in patients treated with PLD have also been reported.¹⁷

The association of oral SCC and long-term treatment with PLD in our patient confirms that this drug may be a cause of secondary head and neck cancer, as highlighted in previous reports.

Learning points

- ▶ Long-term maintenance therapy with pegylated liposomal doxorubicin (PLD) has considerable side effects that include dermatological diseases and, less commonly, stomatitis.
- ▶ PLD may be responsible for squamous cell carcinoma of the oral cavity in patients who do not have any other risk factors.
- ▶ Clinicians should be aware of the fact that long-term exposure to PLD may be a risk factor for secondary cancer in the oral cavity, and head and neck specialist examinations should be included in the follow-up visits of exposed patients.
- ▶ Regular intraoral examination is essential for all patients to ensure early diagnosis of oral conditions.

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Competing interests None.

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