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Clinical Record

Salivary gland tumours as second neoplasms: two cases and literature review

N Zidar, N Gale, A Župevc*, M Žargi*

Abstract

Objectives: Patients who survive malignant tumours have an increased risk of second neoplasms, including those of the salivary glands. Mucoepidermoid carcinoma of the parotid gland is by far the most common type of second salivary gland tumour; other types have rarely been reported. We describe here two patients with a second tumour of the salivary glands.

Case reports: The first patient was a 22-year-old woman with a low grade mucoepidermoid carcinoma of the parotid gland, which developed 21 years after completion of chemoradiotherapy for acute lymphoblastic leukaemia. The second patient was a 40-year-old woman with an epithelial-myoepithelial carcinoma of the buccal mucosa, which arose 11 years after treatment for two malignant neoplasms – retroperitoneal liposarcoma and squamous cell carcinoma of the uterine cervix.

Conclusions: It is mandatory that survivors of cancer should be monitored carefully, so that the complications related to their previous disease and therapy are detected early and managed properly.

Key words: Salivary Gland Neoplasms; Mucoepidermoid Carcinoma; Tumour Metastasis

Introduction

Tumours of the salivary glands account for approximately 6 per cent of head and neck tumours. Two-thirds are benign, the remainder malignant. They occur most commonly in the major salivary glands, particularly in the parotid gland. The peak incidence is in the sixth and seventh decades, but salivary gland tumours may occur over a wide age range, including childhood.[1]

In the majority of patients, the aetiology of salivary gland tumours is unknown. However, some patients have a history of a previous malignant neoplasm.[1,2] New primary tumours occurring after successful treatment of a previous neoplasm are referred to as second (or secondary) tumours. They usually develop years or even decades after treatment of the first neoplasm has been completed. Since the survival of patients with cancer is improving, particularly amongst children, the problem of long-term complications of cancer treatment is becoming increasingly important.[3] The aim of this paper is to report two patients with salivary glands tumours which developed after successful treatment for other malignant neoplasms.

Case reports

Case one

A 22-year-old-woman presented with a six-month history of a swelling above the left mandibular angle. At the age of one year, she had been successfully treated for acute lymphoblastic leukaemia, with chemotherapy and radiotherapy. A left superficial parotidectomy was performed. Three years later, the patient was alive, with no evidence of disease.

Pathological findings. Macroscopically, the tumour was round, 1 cm in diameter, and whitish and soft on the cut surface. It had well defined borders, and the surrounding salivary gland parenchyma showed normal lobular structure. Microscopically, the tumour was well circumscribed, being partially surrounded by a fibrous capsule. It was composed predominantly of intermediate and clear cells and, rarely, squamous cells, plus dispersed, large mucous cells with pale cytoplasm and displaced nuclei (Figure 1) (which showed mucin production on Alcian blue and mucicarmine staining). There were numerous cysts throughout the tumour, filled with eosinophilic material. There was no necrosis or mitoses. The tumour cells were occasionally positive for Ki67. The stroma was focally hyalinised, and heavily infiltrated by plasma cells and lymphocytes. On the basis of these features, a diagnosis of a low grade mucoepidermoid tumour was made.

Case two

A 40-year-old-woman presented with a swelling in her left cheek. Cytological analysis suggested a salivary gland tumour, possibly malignant. The tumour was resected, together with the surrounding mucosa, adipose tissue and buccinate muscle. The resection margins were analysed by frozen section and were free of tumour. Three years later, the patient was alive, with no evidence of disease.

At the age of 29 years, this patient had been treated for a well differentiated liposarcoma of the retroperitoneum plus squamous cell carcinoma of the uterine cervix (stage II). Both tumours had been surgically removed. After surgery, the patient had undergone radiotherapy.

From the Institute of Pathology, Medical Faculty, University of Ljubljana, and the *Department of Otorhinolaryngology and Cervicofacial Surgery, Clinical Center, Ljubljana, Slovenia.
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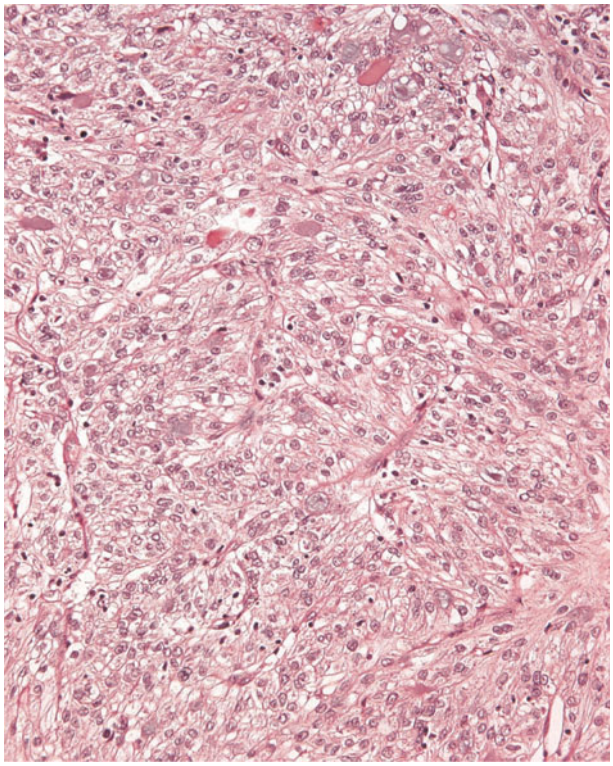

FIG. 1

Low grade mucoepidermoid carcinoma found in patient one. The tumour is composed of intermediate and clear cells and, rarely, squamous cells, plus dispersed, large mucous cells with pale cytoplasm and displaced nuclei (H&E; original magnification ×20).

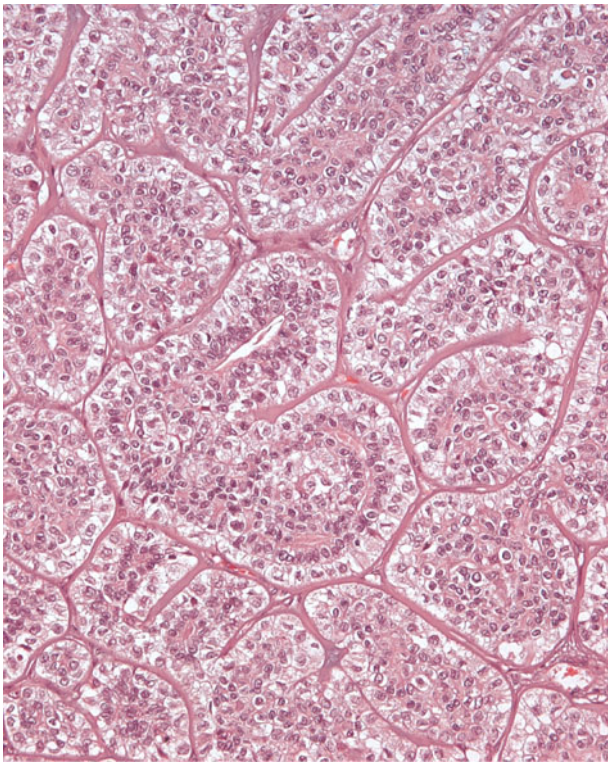

FIG. 2

Epithelial-myoepithelial carcinoma found in patient two. Tumour consists of double-layered, ductal structures; the inner layer is composed of small, eosinophilic cells, and has a surrounding outer layer of larger, polygonal cells with clear cytoplasm (H&E; original magnification ×20).

Liposarcoma recurred eight years later, and was surgically removed.

Pathological findings. Macroscopically, the resected tumour was round, 0.8 cm in diameter, and whitish and firm on the cut surface. Microscopically, the tumour was well circumscribed, being partially surrounded by a thin capsule. It consisted of double-layered, ductal structures; the inner layer was composed of small, eosinophilic cells, and had a surrounding outer layer of larger, polygonal cells with clear cytoplasm (Figure 2). There was focal capsular invasion, but no vascular or perineural invasion was noted. Immunohistochemical analysis indicated that the cells of the inner layer expressed keratin, while the cells of the outer layer expressed α smooth muscle actin and calponin. On the basis of these features, a diagnosis of epithelial-myoepithelial carcinoma was made.

Discussion

Patients who survive malignant tumours have an increased risk of second neoplasms.[3–7] A second (or secondary) neoplasm is defined as a malignant neoplasm in a new location, which is the result of neither direct spread nor metastasis from the primary neoplasm.[7] Both terms – 'second' and 'secondary' – are used for such tumours. We believe that the term 'second tumour' should be used to denote a new primary tumour, whereas the term 'secondary' should be used to imply that the development of the new primary tumour is related to known factors, such as previous treatment for a malignant neoplasm (e.g. radiotherapy or chemotherapy).

Second tumours are among the most important causes of morbidity and mortality in cancer survivors. Their incidence is increasing because the survival rates for childhood cancer have improved to 80–85 per cent, and the proportion of long-term cancer survivors within the general population is increasing every year.[3] The risk of a second malignant tumour in patients treated for childhood cancer is approximately 12 per cent at 20 years, and up to 20 per cent at 25 years.[7,8] The risk of developing another cancer can thus be up to 35 times greater than in the general population. The most common second malignant neoplasms are leukaemia, malignant lymphoma, bone and soft tissue tumours, and carcinoma of the breast, skin, thyroid and salivary gland.[4–7] Second leukaemias, and some second lymphomas, generally demonstrate aggressive behaviour and respond poorly to therapy. In contrast, some second solid neoplasms, particularly of the thyroid and salivary glands, have a good prognosis if diagnosed early, and can be managed successfully by surgery.[8]

Regarding aetiology and pathogenesis, the development of second tumours has been attributed to the effects of ionising radiation, chemotherapy and/or genetic factors.[4,6] Of these, ionising radiation is historically the most studied risk factor. There is compelling evidence implicating accidental and therapeutic exposure to ionising radiation (the latter for treatment of benign and malignant disease) in the development of salivary gland tumours.[1,9] A three-and-a-half- to 11-fold increase in the relative risk of developing salivary gland tumours has been reported in survivors of atomic bomb explosions.[10,11] Therapeutic radiation has been linked to an annual incidence of salivary tumours as high as 77 cases per 100 000 people, compared with 0.6 cases in a non-exposed control group.[1,12] Less

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TABLE I

REPORTED CASES OF SECOND TUMOURS OF THE SALIVARY GLAND, OTHER THAN MUCOEPIDERMOID CARCINOMA

Study	Pts (*n*)	Primary tumour			Second tumour			
		Type	Time interval* (y)	Treatment	Type	Site	Treatment	Follow up
Kaste *et al.*[12]	1	–	–	ChT, RT	ACC	Parotid	Surgery	NED
Whatley *et al.*[29]	1	ALL	15	ChT, RT	ACC	Parotid	Surgery, RT	NED at 9 y
Whatley *et al.*[29]	1	ALL	25	ChT, RT	Pleomorphic adenoma	Parotid	Surgery	Recurrence at 3 y
Hijiya *et al.*[30]	1	ALL	15.6	ChT, RT	ACC	Parotid	–	Alive at 29.2 y
Hijiya *et al.*[30]	1	ALL	18.3	ChT, RT	ACC	Parotid	–	Alive at 18.5 y
Cheuk *et al.*[31]	1	ALL	13	ChT, RT BMT	ACC	Parotid	Surgery, RT	NED
Present	1	Liposarcoma Uterine cervix Ca	12	ChT, RT	Epithelial-myoepithelial Ca	Buccal mucosa	Surgery	NED at 9 y

*Between the development of primary and second tumours. Pts = patients; – = not available; y = years; ChT = chemotherapy; RT = radiotherapy; ACC = acinic cell carcinoma; NED = no evidence of disease; ALL = acute lymphoblastic leukaemia; BMT = bone marrow transplantation

frequently, second salivary gland neoplasms develop in patients who had previously suffered cancer treated by chemotherapy alone, and, exceptionally, in those with previous cancer treated only by surgery.[5,13]

Mucoepidermoid carcinoma is by far the most common type of second salivary gland tumour, with more than 70 cases reported.[12–29] The most frequent primary neoplasm in these patients was acute leukaemia, followed by Hodgkin's lymphoma, sarcoma and brain tumours. The vast majority occurred in the parotid gland; only exceptionally have such tumours been reported in the submandibular gland or minor salivary glands.[5,28,29] The time elapsed between diagnosis of the primary tumour and diagnosis of the second, salivary gland tumour ranged from one to 29 years. Second mucoepidermoid carcinoma typically occurred in patients who had received radiation therapy for their first neoplasm, but there are well documented cases of second mucoepidermoid carcinoma occurring in patients treated only by chemotherapy.[5,12,13,19,23,28,29] The majority of reported cases involved low grade mucoepidermoid carcinoma, with an excellent prognosis after complete removal of the tumour (although some were high grade tumours); only exceptionally did such tumours result in the patient's death.[12,28,29] We describe another patient with low grade mucoepidermoid carcinoma in the parotid gland who had previously undergone chemotherapy and radiotherapy for acute childhood leukaemia.

- **Patients who survive malignant tumours have an increased risk of second neoplasms, including those of the salivary glands**
- **Mucoepidermoid carcinoma of the parotid gland is by far the most common type of second salivary gland tumour**
- **It is mandatory that cancer survivors should be monitored carefully, so that complications related to their previous disease and therapy are detected early and managed properly**

In addition to mucoepidermoid carcinoma, rarely, other tumour types have been reported to develop as second neoplasms of the salivary glands, including acinic cell carcinoma and pleomorphic adenoma.[9,12,29–31] These are summarised in Table I. In the current report, we describe a patient who had previously been treated for two malignant tumours – retroperitoneal liposarcoma and squamous cell carcinoma of the uterine cervix – and who subsequently developed an epithelial-myoepithelial carcinoma of the buccal mucosa. The patient had originally been treated by surgery and irradiation of the abdomen. This case of salivary gland tumour cannot therefore be attributed to previous radiation therapy. This patient was not tested for germline mutations, so the possible role of genetic factors remains unknown.

Conclusion

Improving cancer survival rates, particularly in children and young adults, should not be overshadowed by a high incidence of second neoplasms. However, efforts should be made to reduce the carcinogenicity of current therapies, in particular to limit radiation exposure whenever possible without compromising survival.[5] Long-term survivors of cancer should be monitored carefully, so that complications related to their previous disease and therapy are detected early and managed properly.

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Address for correspondence:
Dr Nina Zidar,
Institute of Pathology,
Medical Faculty,
Korytkova 2,
1000 Ljubljana,
Slovenia.

Fax: +386 1 543 71 01
E-mail: nina.zidar@mf.uni-lj.si

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