CASE REPORT

Systemic lupus erythematosus, pregnancy and carcinoma of the tongue

Jeffrey David Unsworth,¹ Andrew Baldwin,² Louise Byrd³¹Manchester General Hospital, Manchester, UK²Department of Oral and Maxillofacial Surgery, North Manchester General Hospital, Manchester, UK³Department of Obstetrics, St Marys Hospital, Manchester, UK**Correspondence to**

Dr Jeffrey David Unsworth, jeffreyunsworth7@hotmail.com

SUMMARY

We present a case which describes a 29-year-old woman with systemic lupus erythematosus who was treated aggressively with cytotoxic immunosuppression. Five years later and approximately 12 weeks pregnant, she is confirmed as having carcinoma of the tongue. Not wishing to consider termination of her pregnancy, she underwent surgical resection, which included partial glossectomy with microvascular reconstruction. Good oral function (speech and swallowing) was restored within 2 weeks. The pregnancy proceeded relatively uneventfully to 37 weeks gestation when proteinuric hypertension necessitated induction of labour. She remains well with no evidence of recurrence. This case highlights the options available in the treatment of carcinoma of the tongue during pregnancy together with the ethical considerations required, balanced against optimising maternal outcomes.

BACKGROUND

Although rare, oral cancer has been described in pregnancy.¹ Surgical resection of the primary lesion with neck dissection, and reconstruction with microvascular free-tissue transfer is now the preferred treatment for patients with squamous cell carcinoma of the tongue. Radiotherapy is usually reserved for palliation of advanced lesions, those arising from the base of the tongue, and/or as adjuvant treatment. Although case reports of oral carcinoma of the tongue during pregnancy have been reported in the literature, this case adds to what is a limited database, highlighting the link between systemic lupus erythematosus (SLE) and malignancy and also discusses the ethical challenges when planning management during pregnancy.

CASE PRESENTATION

This 29-year-old woman, who smoked 10–12 cigarettes/day, presented to the antenatal clinic at 6 weeks of pregnancy. Five years earlier she had developed a malar rash, suffered from massive pulmonary haemorrhage and developed acute renal failure. She was diagnosed with SLE, and treated aggressively with cyclophosphamide and mesna. At the time of her pregnancy the disease was quiescent, controlled with a combination of azathioprine and prednisolone.

Over the next 4 weeks she was seen at one of the local oral and maxillofacial units as a 2.5 cm × 1 cm nodular erythematous lesion had been identified along the right lateral border of the tongue, which had been present for approximately 4 months (figure 1). There was no palpable lymphadenopathy. A biopsy confirmed squamous cell carcinoma, with early local

Figure 1 Squamous cell carcinoma on right lateral border of tongue.

invasion (T2N0M0-Stage II; refer to figure 2). The options for therapy were discussed and surgery was scheduled. Detailed discussions were held with the woman regarding the possible adverse effects on pregnancy.

TREATMENT

Surgery was performed at 12 weeks of pregnancy. Anaesthesia was induced; arterial and central blood pressures were invasively monitored throughout the operation. The surgery included tracheostomy, right functional/selective neck dissection (levels I–IV), lip split and mandibulotomy, right partial glossectomy, oral reconstruction using a left radial forearm free flap with microvascular anastomoses and a full thickness abdominal skin graft to the forearm donor site.

Her perioperative course was uneventful, although transfusion of three units of blood and four units of fresh frozen plasma was required. Initially nursed on the high dependency unit, an ultrasound scan 2 days following surgery, confirmed a viable pregnancy. She was discharged home 2 weeks after surgery with good oral function (speech and swallowing).

OUTCOME AND FOLLOW-UP

Histology confirmed severe epithelial dysplasia with multifocal invasive, moderately differentiated, squamous cell carcinoma. Resection margins were clear up to 8 mm, with no metastatic spread to cervical lymph nodes. No postoperative radiotherapy was required.

The pregnancy continued without event until 36 weeks gestation, when she developed proteinuric hypertension, necessitating labour induction a week later. She delivered a female infant vaginally, weighing 2630 g and was discharged home 5 days later.

To cite: Unsworth JD, Baldwin A, Byrd L. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008864

T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4a	Tumour invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b	Tumour invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery
NO	No regional lymph node metastases
	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest Dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastases in a lymph node more than 6 cm in greatest dimension
M0	No distant metastases
M1	Distant metastases

Figure 2 Tumor, node, metastasis (TNM) Classification of Oral Malignancy.

She was seen regularly by the maxillofacial team, and 5 years post surgery, there has been no sign of disease recurrence (figure 2). Complete return to normal oral function has been achieved, although some of the wounds have healed with hypertrophic/keloid scar formation (figure 4).

DISCUSSION

Oral cancer is generally considered a disease of later life. However, the incidence of cancer of the tongue has increased among younger patients and, as childbearing has been deferred, intraoral cancers may be seen more frequently in this group.

This woman had several risk factors for developing oral malignancy. First, patients with SLE are at an increased risk of developing malignancy compared with the general population² and several cases of oral and lip cancers associated with lupus have been reported in the literature.³ The cause for this is uncertain due to the complexity of the disease pathophysiology; however, dysregulation of the immune system demonstrated by impaired T-cell receptor signalling, autoantibody production, altered T-cell regulator function and defective cytotoxic T-cell killing may all be implicated.^{4 5} Cytotoxic drugs used in the

treatment of SLE may also induce secondary malignancies, influenced by the intensity of treatment (duration/dose) with recent evidence suggesting that cyclophosphamide in particular may enhance tumour growth⁶ potentially by increasing vascular growth factor expression.⁷ The association between immuno-suppressive therapy and malignancy has also been documented.⁸ Whether the increased risk of malignancy observed in patients with SLE is primarily due to SLE and intrinsic disturbances of immunity predisposing to cancerous mutations, or is secondary to the influence of immunosuppressive/cytotoxic treatment, is unclear. The changes that occur in the immune system during pregnancy its self, particularly in the first 20 weeks, are also potentially capable of promoting neoplastic growth. These changes include increased corticosteroid and human gonadotropins and T-lymphocyte suppression. T helper lymphocytes (CD4) are classified into T helper 1 (Th1) or T helper 2 (Th2) cells dependent on their cytokine profile and function; Th1 cells are predominately involved in cell-mediated immunity while Th2 cells are involved in stimulating humoral immunity. During pregnancy increased levels of progesterone may affect T-cell differentiation, thereby suppressing differentiation along the Th1 pathway in favour of enhancing the Th2 pathway.⁹ Increased Th2 cytokines are thought to inhibit natural killer (NK) cell proliferation and function¹⁰ which are important in tumour immune surveillance, thereby, potentially promoting neoplastic

Figure 3 The tongue postsurgery.

Figure 4 Keloid formation of forearm donor site.

growth. Cigarette smoking is also associated with oral malignancy¹¹; more than likely mediated by impairment of NK cell function.¹² The exact cause of oral malignancy in this woman is probably multifactorial.

Management depends on the type, site and stage of the cancer. During pregnancy, choice of therapy also depends on the stage of pregnancy and the wishes of the mother and her partner. Treatment with surgery alone (resection and reconstruction) or in combination with adjuvant radiotherapy for more advanced lesions (minimal resection margins, and/or positive lymph nodes; 20–30% of T1 and T2 tumours)¹³ is considered the gold standard.¹⁴

The occurrence of cancer during pregnancy, therefore, presents certain therapeutic dilemmas; do we compromise on treatment in favour of the fetus, or optimise treatment accepting an increased risk to the fetus? Extensive surgery in the first trimester may induce spontaneous miscarriage, although the risk of both fetal loss and teratogenicity is negligible. In later pregnancy, local disease may be closely monitored, with early delivery planned; however, more extensive disease may necessitate intervention; surgery at this time may predispose to preterm labour.¹⁴ Overall the second trimester would seem the safest time to perform surgery.

Radiotherapy in pregnancy also poses several problems. During early preimplantation, the principal effect is prenatal death and miscarriage. During major organogenesis (2–7 weeks post conception) the embryo is sensitive to the teratogenic, growth retarding, lethal and postnatal neoplastic effects of radiation. From the 8th to the 40th week there is a decreasing risk of organ malformation, but there is a risk of growth retardation, functional abnormalities (especially of the central nervous system) and postnatal neoplastic development.¹⁵ The precise risk is difficult to calculate, but is dose related; being negligible if doses of 0.1 Gy are not exceeded.¹⁶

Fortunately in this case the cancer was contained and amenable to surgery, albeit radical; radiotherapy was therefore avoided. Some of the wounds healed with hypertrophic scars, related in part to the hormonal influences of pregnancy, in part to her SLE and her ethnicity. Both pregnancy and SLE predispose to a hypercoagulable state, the former by increasing the concentration of clotting factors, reducing thrombolysis and increasing production of platelets, the latter by an increase in thrombophilic abnormalities.¹⁷ However, despite concerns that the vessels used in microvascular anastomoses might have thrombosed, the free-tissue transfer reconstruction worked well. Future close surveillance is vital and continues.

The management of carcinoma of the tongue during pregnancy is complex; dependent primarily on the oncological and surgical assessment of malignancy, treatment also dictates that both the emotional and ethical challenges posed by pregnancy are addressed. From the limited literature available (5 case reports involving 7 patients in total) the majority of patients (5 cases) were successfully treated by surgery alone (resection and reconstruction) with delivery of a healthy baby.^{18–20} In one case, a limited resection was undertaken in order to avoid stress to the fetus; this patient unfortunately died from recurrence.²⁰ The final patient declined surgery, but instead underwent treatment with chemotherapy until 32 weeks gestation and then underwent delivery by caesarean section. This was followed by a course of chemoradiotherapy which induced complete regression of the primary tumour, but subsequently had to undergo bilateral neck dissection and hemiglossectomy due to recurrence.¹⁹

The available data emphasise the delicate balance that exists between fetal and maternal health in this situation. Care must be taken when planning treatment in order to ensure that in

trying to minimise the risks to pregnancy we still strive to optimise outcome for the mother. A multidisciplinary approach, with full and frank discussion, is therefore essential.

Learning points

- ▶ Treatment of choice for patients with squamous cell carcinoma of the tongue involves surgical resection of the primary lesion with neck dissection and reconstruction with microvascular free-tissue transfer plus radiotherapy for more advanced lesions.
- ▶ During pregnancy the risks of treatment to both the mother and her baby should be considered; surgery during the second trimester is safest for pregnancy.
- ▶ To optimise outcomes women should be managed within a multidisciplinary team—to include oral and maxillofacial surgeons, high-risk obstetricians and oncologists.
- ▶ Medical, ethical and emotional factors are all important when planning management in this setting.

Contributors JDU wrote the manuscript and arranged medical illustration digitisation of images. AB critically reviewed the manuscript, in particular the surgical aspects of the case and also consented the patient for photographs and publication. LB critically reviewed the manuscript, in particular the obstetric aspects of the case.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Lloyd CJ, Paley MD, Penfold CN, *et al.* Microvascular free tissue transfer in the management of squamous cell carcinoma of the tongue during pregnancy. *Br J Oral Maxillofac Surg* 2003;41:109–11.
- 2 Bernatsky S, Ramsey-Goldman R, Clarke A. Malignancy in systemic lupus erythematosus: what have we learned? *Best Pract Res Clin Rheumatol* 2009;23:539–47.
- 3 Grimaldo-Carjevski M, Lopez-Labady J, Villarreal-Dorrego M. Squamous cell carcinoma on the palate in a patient with systemic lupus erythematosus: case report and literature review. *Lupus* 2011;20:519–22.
- 4 Lee JH, Wang LC, Lin YT, *et al.* Inverse correlation between CD4⁺ regulatory T cell population and autoantibody levels in paediatric patients with systemic lupus erythematosus. *Immunology* 2006;117:280–6.
- 5 Stohl W, Elliott JE, Li L, *et al.* Impaired nonrestricted cytolytic activity in systemic lupus erythematosus: involvement of a pathway independent of Fas, tumor necrosis factor, and extracellular ATP that is associated with a little detectable perforin. *Arthritis Rheum* 1997;40:1130–7.
- 6 Kempen JH, Gangaputra S, Daniel E, *et al.* Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: a critical assessment of the evidence. *Am J Ophthalmol* 2008;146:802–12.
- 7 Wu YJ, Muldoon LL, Dickey DT, *et al.* Cyclophosphamide enhances tumor growth in nude rat xenografted tumor models. *Neoplasia* 2009;11:187–95.
- 8 Bernatsky S, Ramsey-Goldman R, Clarke A. Exploring the links between systemic lupus erythematosus and cancer. *Rheum Dis Clin North Am* 2005;31:387–402.
- 9 Miyaura H, Iwata M. Direct and indirect inhibition of Th1 development by progesterone and glucocorticoids. *J Immunol* 2002;168:1087–94.
- 10 Seo N, Tokura Y, Furukawa F, *et al.* Down-regulation of tumoricidal NK and NK T cell activities by MHC kb molecules expressed on Th2-type $\gamma\delta$ T and $\alpha\beta$ T cell coinfilting in early B16 melanoma lesions. *J Immunol* 1998;161:4138–45.
- 11 Warnakulasuriya S, Sutherland G, Scully C. Tobacco, oral cancer, and treatment of dependence. *Oral Oncol* 2005;41:244–60.
- 12 Lu LM, Zavitz CC, Chen B, *et al.* Cigarette smoke impairs NK cell-dependent tumour immune surveillance. *J Immunol* 2007;178:936–43.
- 13 McGuirt WF, Johnson JT, Myers EN, *et al.* Floor of mouth carcinoma: the management of the clinically negative neck. *Arch Otolaryngol Head Neck Surg* 1995;121:278–82.
- 14 Palme CE, Gullane PJ, Gilbert RW. Current treatment options in squamous cell carcinoma of oral cavity. *Surg Oncol Clin N Am* 2004;13:47–70A.

- 15 Wong F, Sai-Ki O, Cheung F, *et al*. Pregnancy outcome following radiotherapy for naso-pharyngeal carcinoma. *Eur J Obstet Gynecol Reprod Biol* 1986; 22:157–60.
- 16 Becher MD, Hyman GA. Management of Hodgkin's disease co-existent with pregnancy. *Radiology* 1965;85:725.
- 17 Alfeltra A, Vadacca M, Conti L, *et al*. Thrombosis in systemic lupus erythematosus: congenital and acquired risk factors. *Arthritis Rheum* 2005;53:452–45.
- 18 Atabo A, Bradley PJ. Management principles of head and neck cancers during pregnancy: a review and case series. *Oral Oncol* 2008;44:236–41.
- 19 Layton SA, Rintoul M, Avery BS. Oral carcinoma in pregnancy. *Br J Oral Maxillofac Surg* 1992;30:161–4.
- 20 Yokoshima K, Nakamizo M, Sakanushi A, *et al*. Surgical management of tongue cancer during pregnancy. *Auris Nasus Larynx* 2012;39:428–30.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow