CASE REPORT

Four synchronous cancers in a patient with tongue pain as the only symptom

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SUMMARY

Synchronous carcinomas may be present in up to 6% of patients with head and neck squamous cell carcinoma (HNSCC) and thus may represent a significant factor in the disease burden. This case report illustrates the importance of a thorough examination of these patients. This patient presented with three synchronous squamous cell carcinomas, two in the tongue and one in the aryepiglottic fold. Positron emission tomography CT (PET-CT) was required for the detection of the carcinomas as the initial MRI and CT scans were inconclusive due to artefacts. Furthermore, PET-CT also revealed increased metabolic activity in the lymph nodes of the neck, which subsequently led to detection of a low-grade follicular lymphoma in addition to the squamous cell carcinomas. These findings support a generous use of PET-CT in patients with HNSCC, at least in those with obvious risk factors.

BACKGROUND

Cancer of the head and neck regions remains a significant cause of morbidity and mortality, and a high incidence of second primary carcinomas (SPCs) in this region seems to play an important role in the disease burden.^{1–2} For patients with head and neck squamous cell cancers (HNSCC), synchronous SPC has been reported in 1–6% and metachronous (subsequent) SPC in 20–30%.^{3–4}

Synchronous SPCs are most often located in the head and neck areas, lung and oesophagus.^{2–3–5–7} A few studies have also reported on follicular lymphoma (FL) synchronous to HNSCC.^{8–10} The aetiology of HNSCC in combination with malignant lymphoma is partly unknown, and it remains unresolved if cancer in the aerodigestive tract could be closely related to the coexistence of malignant haemopoietic disease. We report a rare case of a patient diagnosed with four synchronous cancers.

CASE PRESENTATION

A 72-year-old Danish male was referred to a department of otolaryngology because of persistent pain in the left side of the tongue. Clinical examination revealed a tumour that fixated the inferior left side of the tongue to the underlying floor of the mouth and an ulcerative lesion of the mucosa. The patient's appetite was reduced due to tongue pain, but he had not experienced weight loss or other cancer-specific symptoms. He had a history of hypercholesterolaemia, hypertension and atrial fibrillation. He was a cigarette smoker since the age of 16 but had no history of alcohol abuse.

A microscopic diagnosis of squamous cell carcinoma (SCC) was made from incisional biopsies of the lesion. Initial CT and MRI were inconclusive regarding tumour stage due to artefacts (figure 1).

INVESTIGATIONS

The patient was referred to the Head and Neck Cancer Multidisciplinary Team at Odense University Hospital. A second CT scan revealed a tumour that measured 2.7×1.7×1.6 cm. Positron emission tomography CT (PET-CT) demonstrated increased metabolic activity of the tumour localised in the tongue (figure 1), as well as in the aryepiglottic fold on the right side, in lymph nodes on both sides of the neck and in two lymph nodes close to the chest (figure 2). Blood tests revealed no sign of immunodeficiency. Lactate dehydrogenase was not elevated. Previous Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection was identified. HIV status was not investigated.

TREATMENT

Surgical treatment of the tongue cancer was performed as a left hemiglossectomy with a radical resection of the primary tumour and an ipsilateral modified radical neck dissection of levels I–V. The surgical defect was reconstructed using a nasolabial flap. Incisional biopsies were obtained from a 1×1 cm tumour in the aryepiglottic fold, and a lymph node was excised from the right side of the neck.

Histopathology revealed four primary cancers, one SCC on the left side of the tongue (figure 3) and an additional SCC in the fold between the tongue and the floor of the mouth. The two tumours were in close proximity but were two separate entities. A third SCC was found in the right aryepiglottic fold (figure 3). Finally, a grade 2 FL was diagnosed by coincidence in the lymph nodes of the neck. Furthermore, one metastasis from SCC was detected in level II of the left side of the neck, thus classified as pT2N1M0 from the primary tumour of the tongue. The metastasis was without extranodal extension (figure 4). None of the carcinomas showed overexpression of p16, indicating no relation to human papillomavirus (HPV) infection.

The patient was referred for postoperative adjuvant radiotherapy for the metastatic SCC of the tongue including the site with a second primary oral SCC, and the supraglottic carcinoma of the aryepiglottic fold. The patient received definitive radiotherapy with a schedule of five weekly fractions to a total dose of 66 Gy. The patient was in

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Figure 1 Initial CT (A) and MRI (B) with dental artefacts and positron emission tomography CT (C1 and C2) with enhanced metabolic activity of the same area.

good general condition and radical radiation treatment was initiated just three weeks after reconstructive surgery.

A diagnosis of grade 2 FL stage 4a (Ann Arbor classification)¹¹ was made by haematological examination of the bone marrow. The patient was asymptomatic from his low-grade lymphoma and no treatment was indicated.

OUTCOME AND FOLLOW-UP

The patient had full compliance to radiotherapy that ended within 7 weeks according to national standards. Owing to large treatment volumes owing to inclusion of the oral cavity as well as the larynx and elective lymph node regions, a feeding tube was inserted and later removed during follow-up. Twelve

months after the primary diagnosis, the patient is well with no evidence of disease from his three SCCs. He has minor functional sequelae of the mouth, slight dysphagia and xerostomia, but no weight loss. Blood tests have not shown any progression of the FL, and being asymptomatic, no further treatment has been advised.

DISCUSSION

Synchronous SPCs may occur in 1–6% of patients with HNSCC and are thus of significant clinical importance since good treatment options exist and because of their potential detection during investigations of the first primary cancer. In our case, three additional malignancies to a tongue carcinoma were

Figure 2 Positron emission tomography CT showing enhanced metabolic activity of the right aryepiglottic fold (A) and lymph nodes of the neck (B).

Figure 3 Histopathology showing squamous cell carcinomas in the tongue (A) and larynx (B) (x25, H&E).

discovered during the workup investigations. Two were located in the upper aerodigestive tract, which has previously been identified as the most common site of SPC in patients with HNSCC,^{3 6 7 12 13} and the third was a grade 2 FL discovered in the lymph nodes of the neck.

Detection of three adjacent SCCs in the upper aerodigestive tract is in accordance with the concept of field cancerisation. This concept was first described by Slaughter *et al*¹⁴ after discovering the presence of multiple independent tumours and an abnormal epithelium in the mucosa adjacent to primary oral SCCs. Field cancerisation has been explained by (1) single cancer cells or small clusters of cells that migrate through the submucosa to adjacent areas, (2) cells that are shed in the lumen of the specific organ which give the opportunity to regrow normal adjacent tissue and (3) the recent theory describing a large contiguous genetically altered field existing in the epithelium in which multiple clonally related neoplastic lesions may develop.¹⁵ These genetically altered mucosal fields have been described with diameters of >7 cm, which indicates that even the supraglottic carcinoma of the aryepiglottic fold could be related to the tongue cancers.¹⁶ The changes are thought to arise from exposure to carcinogens, in this case primarily tobacco, subsequently inducing dysplastic changes that predispose to the development of malignancy. Several genetic markers have been linked to HNSCC. More than 50% will have mutations in the p53 gene and chromosomal events, such as loss of heterozygosity (LOH), and microsatellite alterations are frequently observed causing genomic instability.¹⁷ Similar genetic changes have been identified in adjacent tissues to the primary

tumours, providing a genetic explanation for the concept of field cancerisation.^{18 19}

Our patient presented with tongue pain as the only symptom. The initial diagnostic CT and MRI scans were inconclusive due to artefacts from metallic dental fillings. This is a common problem,^{20 21} and our case highlights the risk of missing synchronous cancers when relying on these examinations alone for assessing secondary carcinomas or regional metastatic disease. However, a PET-CT scan easily revealed the three coinciding malignancies because of their increased metabolic activity. In the light of the high rate of synchronous cancers in the head and neck regions, a more liberal approach to examination using PET-CT may be relevant, at least in patients with obvious risk factors, primarily a long history of smoking and/or alcohol abuse.

A recent review found PET-CT to be useful in detection of HNSCC and possible metastases as well as SPCs, especially small tumours. Furthermore, PET-CT may contribute with valuable information when planning the treatment of HNSCCs.²²

In patients with synchronous cancers, we recommend a thorough mapping of both the grade and stage of individual malignancies as this enables prioritisation of treatment. This often requires close cooperation between different specialties, which is one of the many benefits of the multidisciplinary cancer teams to which this patient was referred. In our case, treatment was focused on the SCCs as the grade 2 FL prompted no initial treatment.¹¹

To the best of our knowledge, only a few cases with synchronous cancer of the head and neck regions and FL have been described in the literature.⁸⁻¹⁰ This is a rare combination and we did not find any specific relationship between these malignancies. There is no consensus regarding the pathogenesis of FL. A large number of potential risk factors have been suggested, often linked to immunodeficiency,²³ but blood tests did not show any sign of immunodeficiency in our patient. However, of all non-Hodgkin's lymphomas, FL has shown the most consistent association with cigarette smoking,²⁴ which was the case in our patient being a regular smoker.

We reported a rare case of four synchronous malignancies of the head and neck areas. Synchronous cancers most often occur in this area and we believe that this underlines the importance of a thorough examination, including a generous use of PET-CT in patients who present with malignancies of the head and neck regions. Furthermore, when multiple cancers occur, assessment of tumour extension (TNM staging) and prognosis for each individual disease is important to select and prioritise different treatments.

Figure 4 Lymph node showing metastasis from a squamous cell carcinoma as well as a follicular lymphoma (x12.5, H&E).

Learning points

- ▶ Synchronous second primary carcinomas (SPCs) may present in up to 6% of patients presenting with head and neck squamous cell carcinoma (HNSCC).
- ▶ Sometimes, MRI and CT may not be sufficient in detecting HNSCCs and determining the dissemination of HNSCCs, due to artefacts, for example, dental fillings.
- ▶ Positron emission tomography CT easily detects areas of increased metabolic activity and thus represents an effective instrument in the detection of cancer disease and determination of dissemination.
- ▶ Assessment of tumour dissemination and prognosis of individual carcinomas in patients with synchronous SPCs are important when prioritising different treatments.

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