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Head and neck squamous cell cancer associated with lymphoproliferative malignancies is aggressive

L Li, L Hamilton, J Montgomery and M Stewart

Department of Otolaryngology, Queen Elizabeth University Hospital, Glasgow, Scotland, UK

Abstract

Background. Patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia are at an elevated risk of further malignancy. Head and neck squamous cell carcinoma often presents with cervical lymph node metastasis, and can pose a diagnostic challenge in patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia who may have pre-existing palpable neck nodes.

Methods. A retrospective case review of a health board was conducted to identify patients with head and neck squamous cell carcinoma with a previous diagnosis of non-Hodgkin's lymphoma or chronic lymphocytic leukaemia.

Results. Four patients with head and neck squamous cell carcinoma that developed after non-Hodgkin's lymphoma or chronic lymphocytic leukaemia were identified. Two patients had a background of non-Hodgkin's lymphoma treated with chemotherapy. The remaining two patients had a background of chronic lymphocytic leukaemia under active surveillance. Three out of the four patients died within 30 months of diagnosis.

Conclusion. Head and neck squamous cell carcinoma following non-Hodgkin's lymphoma or chronic lymphocytic leukaemia is aggressive. A heightened clinical suspicion is essential to facilitate early diagnosis and treatment of head and neck squamous cell carcinoma in patients with dual pathology.

Clinical Record

Dr L Li takes responsibility for the integrity of the content of the paper

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Author for correspondence:
Dr Lucy Li, Department of Otolaryngology, Queen Elizabeth University Hospital, Glasgow G51 4TF, Scotland, UK
E-mail: Lucy.li2@nhs.net

Introduction

Patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia are at an elevated risk of developing further malignancies, particularly lung cancer and leukaemia.[1–4] Close follow up and active surveillance amongst long-term survivors is essential to ensure secondary cancers are detected at an early, treatable stage.[5] Secondary malignancies are classified into: synchronous tumours, occurring within six months of identification of the index tumour; and metachronous tumours, diagnosed more than six months following the index tumour.[6]

Head and neck squamous cell carcinoma (SCC) often presents with cervical lymph node metastases. Its timely identification can be confounded in the context of a previous diagnosis of non-Hodgkin's lymphoma or chronic lymphocytic leukaemia. Lymphoma represents the second most common neoplasm arising in the head and neck region, accounting for 2–3 per cent of regional malignant tumours,[7] but the co-existence of head and neck SCC and lymphoma is uncommonly described in the literature.[8–17] Most reports describe an incidental diagnosis of lymphoma on histopathological examination, with only a few cases reporting head and neck SCC presenting as a further cancer amongst patients with a pre-existing lymphoproliferative malignancy.[18–20]

We describe four cases of metachronous head and neck SCC and non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, in order to highlight the clinical aggressiveness of SCC in this context. We also aimed to draw attention to the presentation of SCC as a neck mass, a potential misdiagnosis in patients known to have underlying lymphoproliferative disorders.

Materials and methods

Patients diagnosed with head and neck SCC and metachronous non-Hodgkin's lymphoma or chronic lymphocytic leukaemia over a 10-year period, within a single health board, were identified using pathology records. Patient, imaging, histological and treatment characteristics were recorded. Patient-identifiable information was anonymised and records were stored on National Health Service password-protected computers.

Results

Four patients were identified in total between 2006 and 2016. All patients were male. The mean age was 56.5 years (standard deviation = 6.34 years). Each case is discussed in detail below.

Case one

A 63-year-old man presented in 2009 with a right-sided tongue base mass. He had chronic lymphocytic leukaemia diagnosed in 2006 presenting with cervical lymphadenopathy, and was under 'watchful waiting' surveillance. A tongue base biopsy confirmed poorly differentiated SCC with metastatic SCC on fine needle aspiration cytology (FNAC) of a cervical adenopathy, with tumour–node–metastasis (TNM) staging of $T_3N_{2c}M_0$ (*TNM Classification of Malignant Tumours*, seventh edition[21]).

The patient was treated with chemoradiotherapy to the primary site and neck. Following treatment, there was ongoing palpable right-sided cervical lymphadenopathy. An FNAC and core biopsy confirmed the presence of malignant squamous cells. He underwent a selective neck dissection. All 38 nodes showed appearances consistent with chronic lymphocytic leukaemia and there was no evidence of viable SCC present in any of the nodes. Human papillomavirus (HPV) testing was not performed.

Subsequent computed tomography (CT) scanning showed both head and neck SCC and chronic lymphocytic leukaemia disease progression. He was discussed at the head and neck multidisciplinary team meeting and underwent palliative chemotherapy. Survival duration from the time of head and neck SCC diagnosis to death was 30 months.

Case two

A 58-year-old man presented with right-sided throat pain in 2012. He had chronic lymphocytic leukaemia diagnosed in 2008, and was under 'watchful waiting' surveillance. He was subsequently diagnosed with a $T_4N_0M_0$ (*TNM Classification of Malignant Tumours*, seventh edition[21]) SCC of the right retromolar trigone area. Histopathology showed moderately differentiated SCC, HPV-16 and HPV-18 negative. He underwent wide local excision and neck dissection, followed by adjuvant radiotherapy. He became increasingly frail and unwell after treatment. Survival duration from the time of head and neck SCC diagnosis to death was 29 months.

Case three

A 46-year-old man presented with progressive left-sided throat discomfort and dysphagia in 2012. He had undergone bilateral tonsillectomy as a child and was diagnosed with stage 2a non-Hodgkin's lymphoma in 2013. Endoscopic examination of the pharynx showed a mass in the left lateral oropharynx. Histopathology demonstrated a diffuse large B-cell lymphoma. He was treated with six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone ('R-CHOP'), with radiological complete remission following treatment.

The patient was re-referred to otolaryngology in 2016 with new, persistent and progressive cervical lymphadenopathy, with right-sided throat pain and otalgia. An initial core biopsy showed fibrofatty tissue with no evidence of lymphoma. He was observed for a further three months but developed worsening throat pain. Endoscopy identified a 2 cm hard lump in the right tongue base. Biopsies confirmed a basaloid-type SCC, which was HPV-16 positive. Staging on diagnosis was $T_2N_{2c}M_0$ (*TNM Classification of Malignant Tumours*, seventh edition[21]). He was treated with chemoradiotherapy.

Within 11 months, a CT scan demonstrated disseminated metastatic disease. The patient underwent palliative radiotherapy. Survival duration from the time of head and neck SCC diagnosis to death was 27 months.

Case four

A 59-year-old man presented in 2015 with an enlarging left-sided neck mass, a 'hot potato voice' and dysphagia. He was previously diagnosed with stage 2a non-Hodgkin's lymphoma in 2015. On examination, he had a palpable left-sided level II neck node. Flexible nasendoscopy revealed a large tongue base mass confirmed as a diffuse large B-cell lymphoma on biopsy. He was referred to the haematology department and treated with six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone.

The patient underwent a positron emission tomography (PET) scan following completion of chemotherapy, which showed ongoing tongue base asymmetry. A biopsy demonstrated a basaloid-type SCC of the tongue base, which was positive for HPV-16. The FNAC findings of the right lymph node showed appearances consistent with a cystic metastatic SCC. Staging on diagnosis in 2016 was $T_1N_1M_0$ (*TNM Classification of Malignant Tumours*, seventh edition[21]).

The patient was treated with concurrent chemoradiotherapy with curative intent. A follow-up PET scan did not demonstrate any residual abnormal metabolic activity. The patient has since been regularly followed in the ENT out-patient clinic, with no evidence of recurrent disease.

Discussion

This report represents the first report of metachronous, non-cutaneous head and neck SCC in patients with a pre-existing diagnosis of non-Hodgkin's lymphoma or chronic lymphocytic leukaemia in the last 30 years.

- Patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia are at an elevated risk of further malignancy
- Head and neck squamous cell carcinoma (SCC) following lymphoproliferative malignancies is aggressive
- A heightened clinical suspicion is required to facilitate early diagnosis and treatment of head and neck SCC in patients with dual pathology

Our findings highlight the importance of maintaining a heightened index of suspicion for secondary malignancies in patients with a previous diagnosis of a lymphoproliferative disorder. Patients presenting with a neck lump may have their cervical lymphadenopathy wrongly attributed to the underlying lymphoproliferative malignancy, as opposed to head and neck SCC metastasis, which can lead to inaccurate or delayed diagnosis.[18,22] Our case series suggests that these patients have an aggressive head and neck SCC disease course, which potentially indicates a poorer prognosis.

It is very unusual for lymphoproliferative malignancies and head and neck malignancy to occur simultaneously, with an estimated incidence of head and neck SCC second primaries of between 0.2 per cent and 20 per cent.[9,18,23] The largest case series examining patients with a lymphoproliferative malignancy and a second primary SCC in the head and neck was published by Boddie *et al.* in 1977. The average survival duration of patients with metachronous primaries involving the oral cavity, nasal or oral pharynx, hypopharynx, or larynx was 8.5 months.[18] In contrast, the mean survival duration of the three patients that died in our series from the time of head and neck SCC diagnosis was 28.7 months.

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The increased survival duration in our series likely reflects significant advancements in the management of head and neck SCC over the last half century. The patient in case four was most recently diagnosed in 2015, at a time when PET scanning was more readily available, and this is likely to have affected survival.[24] Furthermore, two patients in our case series had HPV-positive oropharyngeal SCC. This is a distinct SCC subtype, which has increased in incidence over the last three decades, and is associated with a better prognosis than HPV-negative disease. This may be due to the increased infiltration of immune cells, particularly $CD8^+$ T-cells in the tumour microenvironment, compared to HPV-negative head and neck SCC.[25]

Although the mechanisms underlying the increased incidence of metachronous cancers in patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia are unknown, multiple theories have been proposed. There is increasing evidence to suggest that people with lymphoproliferative malignancies are immunosuppressed, either by the disease or as a direct result of treatment. Advances in the management of haematological malignancies have also resulted in longer survival duration in patients in an immunocompromised state.[1,9] Other factors include genetic susceptibility, advanced age, infection with an oncogenic virus and environmental exposure to carcinogenic chemicals.[6]

Radiation-induced malignancy can also develop in the area of radiation exposure after a latent period, with an incidence as high as 15 per cent within five years of treatment.[26] Such malignancies may demonstrate atypical clinical and histological features, and the disease may have an aggressive clinical course compared to *de novo* SCCs.[27] Tumour margins may also be difficult to assess when operating on pre-irradiated tissue, and treatment options are limited as most patients would have had radiation doses at the maximal limits of tolerability for their primary malignancy.

In an era where core biopsy is considered diagnostic for lymphoma and SCC, the detection of dual pathology on tissue cores can be problematic. For example, the patient in case one had a core biopsy and FNAC of the level III nodes on his right side that confirmed the presence of malignant squamous cells, but had negative findings for specimens from all 38 nodes on subsequent neck dissection. The diagnosis of SCC following radiotherapy on FNAC or core biopsy can be difficult because of inflammation and necrosis following treatment, resulting in fibrosis and decreased cellularity.[28] Cell viability within an FNAC sample may also be difficult to assess, given that viable SCC may be degenerate, cystic or necrotic in appearance.[29]

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Competing interests. None declared

References

1 Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. *Br J Cancer* 2001;**85**:997–1005
2 Mudie NY, Swerdlow AJ, Higgins CD, Smith P, Qiao Z, Hancock BW *et al.* Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. *J Clin Oncol* 2006;**24**:1568–74
3 Brennan P, Scélo G, Hemminki K, Mellemkjaer L, Tracey E, Andersen A *et al.* Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma. *Br J Cancer* 2005;**93**:159–66
4 Schöllkopf C, Rosendahl D, Rostgaard K, Pipper C, Hjalgrim H. Risk of second cancer after chronic lymphocytic leukemia. *Int J Cancer* 2007;**121**:151–6
5 Petrakova K, Vyskocil J, Grell P, Majek O, Soumarova R, Novak J *et al.*. Second cancers in Hodgkin's lymphoma long-term survivals: a 60-year single institutional experience with real-life cohort of 871 patients. *Int J Clin Pract* 2018:e13235
6 Moertel CG. Multiple primary malignant neoplasms: historical perspectives. *Cancer* 1977;**40**:1786–92
7 DePeña CA, Van Tassel P, Lee YY. Lymphoma of the head and neck. *Radiol Clin North Am* 1990;**28**:723–43
8 Joo Y-H, Jung C-K, Sun D-I, Kim M-S. Synchronous laryngeal squamous cell carcinoma and Hodgkin lymphoma of the head and neck region. *Auris Nasus Larynx* 2009;**36**:501–4
9 Perez-Reyes N, Farhi DC. Squamous cell carcinoma of head and neck in patients with well-differentiated lymphocytic lymphoma. *Cancer* 1987;**59**:540–4
10 Stack BC, Ridley MB, Endicott JN. Simultaneous squamous cell carcinoma of the head and neck and reticuloendothelial malignancies. *Am J Otolaryngol* 1996;**17**:178–83
11 Watanabe N, Inohara H, Akahani S, Yamamoto Y, Moriwaki K, Kubo T. Synchronous squamous cell carcinoma and malignant lymphoma in the head and neck region. *Auris Nasus Larynx* 2007;**34**:273–6
12 Hammami B, Mnejja M, Achour I, Chakroun A, Khabir A, Chakroun A *et al.* Association of squamous cell carcinoma of the larynx and chronic lymphoid leukemia. *Eur Ann Otorhinolaryngol Head Neck Dis* 2010;**127**:153–5
13 McElroy C, Velilla R, Chaudhary H, Al-Abbadi MA. Fine-needle aspiration diagnosis of squamous cell carcinoma in a lymph node involved with small lymphocytic lymphoma: case report and review of the literature. *Diagn Cytopathol* 2009;**37**:48–50
14 Minca EC, Popat SR, Chadha MK, Merzianu M. Small lymphocytic lymphoma obscuring microscopic tonsillar squamous cell carcinoma: an unknown occurrence with a known primary. *Head Neck Pathol* 2012;**6**:125–9
15 Katou A, Hirohata H, Uchida F, Takeuchi Y, Yamato M, Ishibashi-Kanno N *et al.* A rare case of synchronous squamous cell carcinoma on the body of the tongue and malignant lymphoma of the neck. *J Dents Dent Med* 2018;**1**:110
16 Singh NJ, Tripathy N, Roy P, Manikantan K, Arun P. Simultaneous triple primary head and neck malignancies: a rare case report. *Head Neck Pathol* 2016;**10**:233–6
17 Tezer MS, Tuncel U, Uzlugedik S, Uzun M, Kulaçoğlu S, Unal A. Coexistence of laryngeal squamous cell carcinoma and non-Hodgkin's lymphoma with nasopharyngeal involvement. *J Laryngol Otol* 2006;**120**:e2
18 Boddie AW, Goepfert H, Fischer EP, Ballantyne AJ. Head and neck cancer developing in patients with pre-existing reticuloendothelial malignancies. *Laryngoscope* 1977;**87**:2090–5
19 Mullen JL, Reichman J, Rosato EF. Multiple carcinomas following therapy for Hodgkin disease. *J Surg Oncol* 1979;**11**:75–8
20 Bakri K, Shimaoka K, Rao U, Tsukada Y. Adenosquamous carcinoma of the thyroid after radiotherapy for Hodgkin's disease. A case report and review. *Cancer* 1983;**52**:465–70
21 Sobin LH, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 7th edn. Chichester: Wiley-Blackwell, 2009
22 Kader I, Leavers B, Shashinder S, Wylie B, Chi K-K, Sundaresan P. Synchronous or metachronous lymphoma and metastatic cutaneous squamous cell carcinoma in the head and neck region: a diagnostic and management dilemma. *J Laryngol Otol* 2016;**130**(suppl 4):S45–9
23 van Leeuwen FE, Klokman WJ, Hagenbeek A, Noyon R, van den Belt-Dusebout AW, van Kerkhoff EH, *et al.* Second cancer risk following Hodgkin's disease: a 20-year follow-up study. *J Clin Oncol* 1994;**12**:312–25
24 Morgan RL, Eguchi MM, Mueller AC, Daugherty SL, Amini A, Karam SD. Imaging at diagnosis impacts cancer-specific survival among patients with cancer of the oropharynx. *Cancer* 2019;**125**:2794–802
25 Reusser N, Downing C, Guidry J, Tyring S. HPV carcinomas in immunocompromised patients. *J Clin Med* 2015;**4**:260–81
26 Tay GC-A, Iyer NG, Ong W-S, Tai D, Ang M-K, Ha TC *et al.*. Outcomes and prognostic factors of radiation-induced and de novo head and neck squamous cell carcinomas. *Otolaryngol Head Neck Surg* 2016;**154**:880–7
27 Levi F, Randimbison L, Te VC, La Vecchia C. Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br J Cancer* 1996;**74**:1847–50
28 Barker HE, Paget JTE, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nat Rev Cancer* 2015;**15**:409–25
29 Paksoy N, Ozbek B. Cytopathologist-performed and ultrasound-guided fine needle aspiration cytology enhances diagnostic accuracy and avoids pitfalls: an overview of 20 years of personal experience with a selection of didactic cases. *Cytojournal* 2018;**15**:8

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