Novel diagnostic procedure

Human papilloma virus: differentiating new primary lung cancer versus metastatic disease from previous head and neck squamous cell carcinoma

Meredith E Giuliani,^{1,2} Ilan Weinreb,³ Andrew J Hope^{1,2}¹Radiation Medicine Program, Princess Margaret Hospital, Toronto, Ontario, Canada;²Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada;³Department of Pathology, University Health Network, Toronto, Ontario, Canada

Correspondence to: Andrew J Hope, Andrew.Hope@rmp.uhn.on.ca

Summary

Distinguishing new primary lung tumours from lung metastasis in patients with head and neck squamous cell carcinoma (SCC) is a challenging clinical problem. Histological examination is not always able to distinguish between these scenarios as SCC is common in both sites. Here the authors present a case of metachronous cancers of the head and neck and lung in which human papilloma virus testing was proposed as a mechanism to distinguish primary from metastatic carcinoma.

BACKGROUND

In the head and neck cancer population, a metachronous tumour in the lung is a challenging clinical problem. This metachronous tumour could represent metastatic disease from the previous head and neck tumour or a primary lung carcinoma. In initial staging for head and neck carcinoma, synchronous metastases are found in 2–17% of patients and lung is the most common site of disease.^{1–2} The lung is also the most common site for second primary tumours in the head and neck squamous cell carcinoma (HNSCC) population.³ Histopathological analyses have limited ability to distinguish metastatic disease from second primary tumours in this setting as the majority (>80%) of head and neck carcinomas⁴ and 24% of lung carcinomas are squamous cell carcinoma (SCC).⁵ Molecular markers such as human papilloma virus (HPV) may assist in distinguishing metastatic from second primary tumours in the lung.⁶ Here we present a case of metachronous HPV positive tumours in the head and neck and lung.

CASE PRESENTATION

A 49-year-old Caucasian man, lifelong non-smoker with no previous medical problems, presented with fullness in his right neck. Examination revealed an enlarged right tonsil, which was removed via tonsillectomy. Histopathology demonstrated a non-keratinising, poorly differentiated SCC. The primary lesion was 4.0 cm in maximal diameter with no lymphovascular or perineural invasion. The tumour was positive for HPV subtype 16 using PCR by linear array.

Further staging investigations, including a PET-CT, demonstrated a conglomerate right level 2⁷ nodal mass. No other sites of metastatic disease were identified. The tumour was staged IVA (T2 N2A M0). The patient subsequently received concurrent chemoradiation. He received 7000 cGy in 35 fractions of external beam radiotherapy to the gross nodal disease and 5600 cGy in 35 fractions to

bilateral neck levels II–V, bilateral retropharyngeal lymph nodes and ipsilateral level 1B⁷ concurrent with cisplatin chemotherapy. Post-treatment PET-CT at 3 months demonstrated no evidence of residual disease and no evidence of distant metastases.

Six months after treatment, an asymptomatic, 4.0 cm left lower lobe tumour was identified on follow-up CT (figure 1). Neither physical exam nor restaging studies including a CT of the head and neck revealed any other sites of disease. The patient was seen by both a thoracic surgeon and a thoracic radiation oncologist. As the lung lesion was solitary and amenable to surgical resection, a diagnostic and therapeutic surgical procedure was planned. The patient underwent left lower lobe superior segmentectomy and medial basal segmentectomy. Pathology from this procedure demonstrated a 3.0 cm × 5.0 cm × 2.7 cm SCC. If staged as a primary lung malignancy, this lesion would be stage group IB (T2aN0M0). Of note, the lesion had positive immunohistochemical staining for p16 (figure 2) and HPV16 DNA. The patient remains free of disease 18 months from his resection.

DISCUSSION

HPV positive HNSCC have improved prognosis over HPV negative HNSCC.^{8–9} As more patients are cured of their primary tumour, the management of subsequent metachronous lung lesions will become increasingly relevant.

The ability to accurately distinguish second primary tumours from lung metastasis in patients with HNSCC is challenging. However, optimal patient management may be dependent on our ability to distinguish between these two scenarios. Histological examination of the tumours is not always able to provide distinguishing information. Further investigations to distinguish metastatic carcinoma from a second primary tumour could include molecular and genetic analyses of both carcinomas. If genetic expression is maintained in metastatic deposits from the original

Figure 1 (A) Axial CT scan of the thorax at initial staging. (B) Axial CT scan of the thorax at follow-up demonstrating a new lung lesion.

tumour, this type of analysis may assist in distinguishing second primary tumours from metastatic disease.¹⁰

HPV is a double-stranded DNA virus and over 100 different subtypes have been identified.¹¹ HPV infection is associated with cancers of the genital tract.¹² HPV subtypes 16, 18, 31, 33 and 45 are most frequently associated with malignancy and subtypes 6 and 11 are most frequently associated with benign conditions, such as condyloma accuminata.¹¹ HPV is also associated with HNSCC. The incidence of HPV infection is high in oropharyngeal tumours (36%)¹³ and in the case of tonsillar carcinoma, up to 53% of tumours demonstrate infection with HPV.¹² The most common HPV subtype in HNSCC is 16.¹³

HPV may be a useful tool to differentiate secondary lung cancers from metastatic disease in patient with HNSCC. If the lung carcinoma is SCC, HPV analyses could be performed. The prevalence of HPV infection is high in HNSCC, especially oropharyngeal cancers, and lower in lung carcinoma; therefore, it can be inferred that HPV positivity is likely more specific for metastatic disease.¹² In one study of patients with lung tumours as well as primary

tumours of the head and neck or female genital tract, identical HPV subtypes were found in 14% of patients, discordant HPV status was found in 43% and no HPV was found in 43%. The authors concluded that HPV was a diagnostic tool, which allowed for definite distinction of metastatic disease from second primary tumours in 57.1% of patients.⁶ In adenocarcinoma, markers such as thyroid transcription factor-1 are similarly useful for distinguishing lung primary tumours from metastatic adenocarcinoma from other sites.⁶

However, if HPV positive lung cancers are more frequent, caution must be exercised when classifying metastatic disease as demonstrated by our case of a young, non-smoking patient. HPV positivity in both tumours does not necessarily indicate metastatic disease. Recently, the role of HPV as an etiological factor in lung cancer has been proposed. The most common etiological factor for the development of lung cancer is tobacco smoking.¹⁴ However, in non-smokers HPV infection may be an important etiological factor.¹⁵ The incidence of HPV infection in bronchopulmonary carcinoma is variable depending on geographic location. In a

Figure 2 (A) p16 immunohistochemistry of the tonsil carcinoma. (B) p16 immunohistochemistry of the lung carcinoma.

2009 review article, 25% of lung cancers were HPV positive. The incidence was lowest in the United States (15%) and highest in Asia (36%).¹⁴ The mechanism of exposure of lung parenchyma to HPV is uncertain. Direct mucosal contact is the usual mechanism for HPV transmission¹⁶; however, this is not possible in the lung.¹⁴ Two proposed hypotheses regarding the mechanism of exposure are the inhalation of infected cells into the periphery of the lung¹⁴ or dissemination via the blood stream from distant mucosal infection.¹⁷

While HPV may provide additional useful information, the entire clinical case must be considered when attempting to determine if a lung lesion represents metastatic disease or a second primary tumour as this decision will alter patient management. If wrongly classified, patients with potentially curable lung tumours may be managed with palliative intent. In the absence of diagnostic certainty, it may be appropriate to give the 'benefit of the doubt' and proceed with curative treatment until future research allows us to classify metachronous lesions with certainty.

Even in those circumstances where molecular or genetic analysis suggests metastatic disease, metastatectomy may be considered in a research context as the natural history of HPV positive HNSCC is still being elucidated.

In conclusion, HPV may be a useful marker to distinguish second primary lung cancers from metastatic disease in patients with HNSCC. However, HPV positivity in tumours of the head and neck and lung does not necessarily indicate metastatic disease, especially in never smokers, and the entire clinical picture must be used to make management decisions.

Learning points

- ▶ HPV is an important etiological factor in HNSCC.
- ▶ HPV DNA provides an additional molecular signature that may assist in distinguishing second primary lung cancers from metastatic disease in patients with HNSCC.
- ▶ HPV positivity in metachronous lung tumours is not pathognomonic of metastatic disease.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **de Bree R**, Deurloo EE, Snow GB, *et al.* Screening for distant metastases in patients with head and neck cancer. *Laryngoscope* 2000;**110**(3 Pt 1): 397–401.
2. **Jäckel MC**, Rausch H. Distant metastasis of squamous epithelial carcinomas of the upper aerodigestive tract. The effect of clinical tumor parameters and course of illness. *HNO* 1999;**47**:38–44.
3. **Jäckel MC**, Reischl A, Huppert P. Efficacy of radiologic screening for distant metastases and second primaries in newly diagnosed patients with head and neck cancer. *Laryngoscope* 2007;**117**:242–7.
4. **Davies L**, Welch HG. Epidemiology of head and neck cancer in the United States. *Otolaryngol Head Neck Surg* 2006;**135**:451–7.
5. **Yang P**, Allen MS, Aubry MC, *et al.* Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. *Chest* 2005;**128**:452–62.
6. **Weichert W**, Schewe C, Denkert C, *et al.* Molecular HPV typing as a diagnostic tool to discriminate primary from metastatic squamous cell carcinoma of the lung. *Am J Surg Pathol* 2009;**33**:513–20.
7. **Grégoire V**, Levendag P, Ang KK, *et al.* CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. *Radiother Oncol* 2003;**69**:227–36.
8. **Ang KK**, Harris J, Wheeler R, *et al.* Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;**363**:24–35.
9. **Sedaghat AR**, Zhang Z, Begum S, *et al.* Prognostic significance of human papillomavirus in oropharyngeal squamous cell carcinomas. *Laryngoscope* 2009;**119**:1542–9.
10. **Perou CM**, Sørli T, Eisen MB, *et al.* Molecular portraits of human breast tumours. *Nature* 2000;**406**:747–52.
11. **Longworth MS**, Laimins LA. Pathogenesis of human papillomaviruses in differentiating epithelia. *Microbiol Mol Biol Rev* 2004;**68**:362–72.
12. **Will C**, Schewe C, Petersen I. Incidence of HPV in primary and metastatic squamous cell carcinomas of the aerodigestive tract: implications for the establishment of clonal relationships. *Histopathology* 2006;**48**:605–7.
13. **Kreimer AR**, Clifford GM, Boyle P, *et al.* Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:467–75.
14. **Klein F**, Amin Kotb WF, Petersen I. Incidence of human papilloma virus in lung cancer. *Lung Cancer* 2009;**65**:13–18.
15. **Cheng YW**, Wu MF, Wang J, *et al.* Human papillomavirus 16/18 E6 oncoprotein is expressed in lung cancer and related with p53 inactivation. *Cancer Res* 2007;**67**:10686–93.
16. **Stanley MA**, Pett MR, Coleman N. HPV: from infection to cancer. *Biochem Soc Trans* 2007;**35**(Pt 6):1456–60.
17. **Chiou HL**, Wu MF, Liaw YC, *et al.* The presence of human papillomavirus type 16/18 DNA in blood circulation may act as a risk marker of lung cancer in Taiwan. *Cancer* 2003;**97**:1558–63.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 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.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Giuliani ME, Weinreb I, Hope AJ. Human papilloma virus: differentiating new primary lung cancer versus metastatic disease from previous head and neck squamous cell carcinoma. *BMJ Case Reports* 2011;10.1136/bcr.09.2010.3377, date of publication

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