CASE REPORT

Small cell neuroendocrine carcinoma of tracheostomy site in a patient with a history of juvenile laryngeal papillomatosis

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SUMMARY

Juvenile laryngeal papillomatosis is the commonest cause of benign epithelial tumours of the larynx. Following diagnostic biopsy, surgical debulking is the mainstay of therapy. The condition is often recurrent with further papillomas forming after debridement, requiring serial procedures and occasionally demanding tracheostomy. Rarely, the disease can undergo malignant transformation; most commonly to squamous cell carcinoma. We describe the first reported case of small cell neuroendocrine carcinoma occurring in the previous tracheostomy site of a 29-year-old male with a history of juvenile laryngeal papillomatosis. The patient, with a background of multiple treatments for juvenile papillomas, presented with voice change, breathing difficulty and erythema at the site of previous tracheostomy. Induction chemotherapy followed by chemoradiation was used to treat the lesion with a good response to initial therapy.

BACKGROUND

Laryngeal papillomatosis (LP) is a rare condition that can affect children (juvenile laryngeal papillomatosis (JLP)) or adults (adult laryngeal papillomatosis).¹ It can occur at any point in the airway but most commonly affects the larynx.² The condition is associated with human papillomavirus (HPV) with subtypes 6 and 11 the most commonly implicated.²

Most cases of juvenile papillomatosis present with voice change or airway compromise before the age of 10 years.³ LP is a benign process which affects the voice and airway secondary to laryngeal involvement. In rare aggressive cases which progress to tracheal and pulmonary involvement, significant respiratory compromise and even death can result.⁴ The aim of treatment is to maintain a patent airway with minimal damage to the underlying normal tissue. Papillomas frequently recur after treatment and this recurrence rate is higher in JLP.¹ Children with JLP often experience remission after a number of years which is thought to be related to puberty, by this time they have normally undergone multiple procedures.

Although laryngeal papillomas are benign, malignant transformation has been reported in 3% to – 6% of cases.^{1 3 5} All cases described to this point have resulted in squamous cell carcinoma. Although it is unclear how this malignant transformation occurs, factors such as smoking and radiation are thought to play a role.² No cases of small

cell carcinoma in patients treated for JLP have previously been described.

CASE PRESENTATION

A 29-year-old male smoker with a history of JLP presented to the ear, nose and throat department with recent voice change and increasing dyspnoea. He first presented with dysphonia at age 3. The diagnosis of JLP was made at laryngoscopy and confirmed histologically on biopsy. On many occasions he was found to have extensive, multifocal disease affecting the tongue base, epiglottis and vocal cords. He underwent regular microlaryngoscopy and removal of papilloma almost on an annual basis. During childhood he also required three tracheostomies for airway protection. The tracheostomies were successfully removed each time. He also underwent interferon therapy in the early 1990s, an approach thought to reduce the frequency of surgical interventions. He was not treated with cidofovir, an antiviral that has been associated with malignant transformation in the past.^{6 7}

By 2012, aged 26, the lesions were seen to be affecting his larynx, oral cavity, subglottis and trachea but were still successfully treated with microdebridement. He did not attend the planned debridement surgery in 2013 at which point he was lost to follow-up.

His general practitioner recontacted our department in 2015 as he was having significant voice difficulties and intermittent airway obstruction with erythema around the previous tracheostomy scar. On examination he was found to have an enlarging 2 cm subcutaneous mass underlying the previous surgical scar. His voice was breathy and rough, consistent with papillomatous disease. He tolerated flexible bronchoscopy in the clinic after administration of lidocaine spray. The findings were of papilloma recurrence on the laryngeal surface of his epiglottis and below the right vocal cord and also an ulcerative tracheal mass at the level of previous tracheostomy.

INVESTIGATIONS

A CT scan revealed a 4×2 cm contrast-enhancing mass extending from the skin to surround the trachea with tracheal narrowing (figure 1).

Biopsy of the lesion showed features of a poorly differentiated carcinoma. The immunophenotype was that of a small cell neuroendocrine carcinoma (cytokeratin paranuclear dot-positivity, CD56

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Figure 1 Top: axial CT scan showing an enhancing mass (circled) extending from the skin surface posteriorly to surround the trachea on the right side. Level C6. Bottom: post-treatment axial CT scan showing disease resolution.

positive, synaptophysin positive, thyroid transcription factor-1 positive). Interestingly, there was some degree of strong staining with p16 which prompted consideration for a possible role of high-risk HPV (HRHPV; [figure 2](#)). A positron emission tomography (PET) scan was performed which confirmed uptake of tumour in the trachea but no nodal or distant metastases.

HPV subtyping by PCR was performed on formalin-fixed paraffin-embedded material from the current sample and two previous histologically confirmed squamous papilloma samples from the same patient taken in 2007 and 2012. The previous squamous papilloma samples were both positive for HPV6 and showed no evidence of HRHPV. Viral subtyping on the most recent small cell neuroendocrine carcinoma biopsy was, on the other hand, positive for HPV 18, a known HRHPV type, and showed no evidence for HPV6.

Figure 2 Top left: H&E×200. Tracheal biopsy showing monomorphic population of small malignant cells. Top right: AE1/3 immunohistochemistry×200. Cytokeratin positive with paranuclear dot-positivity. Bottom left: CD56 immunohistochemistry×200. Diffuse positive staining with neuroendocrine marker CD56. Bottom right: p16×200. Strong staining with p16 prompted consideration for high-risk human papillomavirus-driven disease.

DIFFERENTIAL DIAGNOSIS

The most likely differential diagnosis was that of squamous cell carcinoma given the suspicious features of the lesion and the fact the malignant transformation to small cell cancer (SCC) is a recognised feature of JLP. Further differentials would include malignancy of other cell origin and granulomatous inflammation.

TREATMENT

The patient was diagnosed with small cell neuroendocrine carcinoma of trachea. The multidisciplinary team management's recommendation was for neoadjuvant chemotherapy with cisplatin and etoposide and to assess his response. After two cycles he showed partial response so went on to complete the full course of concurrent chemoradiation with four cycles of cisplatin and etoposide followed by 6 weeks of intensity-modulated radiotherapy.

OUTCOME AND FOLLOW-UP

At the completion of treatment he was found to have achieved a radiological and clinical complete response as assessed by CT and PET. However, 3-month post-treatment PET scan showed uptake in S1 vertebrae and further imaging demonstrated three irregular solid-cystic foci within the posterior cranial fossa consistent with brain metastases. Breakdown at the tracheostomy site was suggestive of local recurrence. He went on to receive palliative radiotherapy as best supportive care.

DISCUSSION

This is the first reported case of a small cell carcinoma arising in the site of JLP. Both subtypes HPV6 and HPV18 have been found in our patient. HPV6 was found in the two previous papilloma samples. HPV6 is the most common HPV subtype found in JP: having a prevalence of 50–84% and HPV11 of 25–37%.⁸ Both HPV6 and HPV11 have been associated with malignant transformation to SCC, although HPV11 is considered to be at higher risk.² Currently, it is unclear how HPV infection can lead to malignancy. Although smoking and irradiation may induce malignant transformation cases have been reported in the absence of these factors. It has been suggested that the virus may incidentally integrate into host genes that are actively transcribed and contribute to neoplastic changes.^{2 9}

In our case, HPV18 was found in the small cell neuroendocrine carcinoma biopsy. Experience of HPV infection of the uterine cervix has shown that multiple HPV strains can coexist.¹⁰ Therefore, it is possible that our patient had been harbouring both subtypes of the virus. There are currently no documented cases of HPV-related small cell carcinoma of the trachea.

Primary tracheal malignancy itself is rare with an estimated incidence of 0.1/100 000 persons/year. Neuroendocrine tumours make up 9.7% of these and are described as carcinoid, atypical carcinoid, small cell carcinoma and combined small cell carcinoma, as per the WHO 2015 report, with the small cell subtype being the least common.

As the small cell subtype is so rare, there are no clear guidelines for treatment. Heikal¹¹ reviewed the literature from 1969 to 2011 and found only 74 cases of small cell neuroendocrine carcinoma of the trachea described in the literature. An updated study in 2015 reported an additional 19 cases.¹² These studies have shown that overall survival is poor and suggest that early diagnosis is the best indicator of prognosis. There is no literature examining a link between HPV and small cell carcinoma of the trachea. Most authors recommend treatment with concurrent chemoradiation with surgical therapy considered if possible given the anatomical constraints of the area.¹²

HPV has been associated with small cell carcinoma at other sites including the oropharynx. Subtypes 16, 18 and 33 have been identified at this site.^{13 14} HPV has also been associated with small cell neuroendocrine carcinoma of the cervix with subtypes 18 and 16 reported in up to 40% of cases.¹⁵ Little is known about HPV as a driver for neuroendocrine tumours at other sites. A recent study into HPV and small cell lung cancer examined 20 surgical specimens for evidence of HPV infection, not a single case was found. The authors concluded that HPV infection is not related to the pathogenesis of small cell lung cancer.¹⁶

HPV infection appears to have been related to oncogenic changes in this patient and as such raises the question whether small cell carcinoma of the trachea is HPV related. It is unclear whether this is a case of malignant transformation or a coincidental primary at the very same location as previous LP.

Patient's perspective

The diagnosis was rather scary even for someone with my medical history as not a lot is known if any about this cancer but luckily I have an excellent medical team who explained fully that things could go either way as they just did not know enough but I stayed positive and am fighting my way through. Treatment was hard but I think I was lucky as my side effects were not too severe. I found my hardest day on chemotherapy was day 2 of my cycle as day 1 was long and the cisplatin made me feel sick but I found if I took my strong sickness tablet at night just before I went to sleep it helped a lot the next day I also used cannabis to ease the nausea and boost my appetite. I know this is not approved but it helped me a lot!! Radiotherapy was a lot easier for me but I think this was due to previous damage to my throat preventing a lot of the pain I managed to stay on a normal diet throughout. The mask fitting is a little strange and not the most comfortable thing to wear but it is only a short time each day. I think the thing that helps the most is the extremely dedicated staff and a positive mental attitude.

Although the reported case may represent a small cell carcinoma which is unconnected to known LP, here we highlight a potential link that has not previously been investigated. The case also highlights that although LP is a benign disease, there is a potential for malignant transformation and although rare, regular follow-up and intermittent biopsies should be the mainstay of treatment to monitor for this. Rapidly progressive or new symptoms warrant urgent investigation.

Learning points

- ▶ Laryngeal papilloma is the most common benign epithelial tumour of the trachea.
- ▶ Main risk is of airway compromise secondary to obstruction by papillomas, commonly at the larynx.
- ▶ The risk of malignancy is low but the index of suspicion must remain high for the treating clinicians.
- ▶ SCC is the most common histological subtype and this is the first case of small cell carcinoma described.
- ▶ Regular follow-up with intermittent biopsies is recommended.

Competing interests None declared.

Patient consent Obtained.

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