CASE REPORT

Suppression of respiratory papillomatosis with malignant transformation by erlotinib in a kidney transplant recipient

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SUMMARY

A 52-year-old non-smoker and renal transplant recipient developed an incessant cough. A CT scan of the thorax revealed ill-defined hazy opacities in the right upper lung. He was diagnosed with non-tuberculosis *Mycobacterium chelonae/abscessus* infection based on sputum culture results. A trial of antibiotics initially resulted in some clinical improvement. A subsequent CT of the thorax documented worsening of the lesions in the right lung and new lesions on the left. An intratracheal growth was noted. Bronchoscopy with biopsy of the tracheal lesions documented respiratory papillomatosis with transformation to squamous cell cancer. Test for high-risk human papilloma virus was positive. Video-assisted thoracoscopic surgery biopsy with wedge resection of the left lower lobe revealed metastatic squamous cell lung cancer. He was treated with one ablation followed by four cycles of chemotherapy. He has been maintained on erlotinib ever since. There has been no recurrence of the cough or papillomas.

BACKGROUND

Respiratory papillomatosis is a rare condition characterised by proliferation of papilloma driven by the human papilloma virus (HPV) in the respiratory tract. Primarily, it is found in the larynx. It may, however, extend down into the lower airways and the lungs occasionally. The overall incidence is higher in the paediatric population (40/million) than in adults (19/million).¹ It is often recurrent and refractory to treatment. Thus, it poses a significant burden to the healthcare system. Depending on the age of diagnosis, it is classified as juvenile (children having a bimodal distribution with higher incidence in those younger than 1-year-old or between the age of 13 and 20) and adult type.² The former type often acquires the virus vertically whereas the latter from having oral sex or multiple sex partners. Gastro-oesophageal reflux disorder is a risk factor.³ The genotypes of HPV can be as many as 130; however, HPV 6 and 11 subtypes are responsible for 90% of all cases of benign papillomas. The remaining cases are caused by other HPVs. High-risk HPV 16 and 18 are associated with most of the malignant transformation, which are responsible for cervical cancer and some oral pharyngeal squamous cell cancer. HPV infection is also responsible for squamous anal cancer that is the second for incidence in patients positive for HIV infection.

Clinically, patients present with non-specific symptoms including hoarseness, cough, stridor, dyspnoea or respiratory distress mostly due to recurrent obstruction. Early stage disease, however, can be a diagnostic challenge. Morbidity and mortality result from airway obstruction or malignant transformation into squamous cell carcinoma and metastasis.⁴ Imaging studies in early stages are rarely revealing. Immunosuppression is a known risk factor for disease progression.⁵ Repeated surgical debulking plus or minus intralesional injection with interferon or cidofovir has been the mainstay of treatment so far, although new drug combinations are showing some promise.⁶ Infection with high-risk HPV may lead to malignant transformation into squamous cell carcinoma.

CASE PRESENTATION

A 52-year-old Asian man developed a cough in July of 2009. The cough was dry initially and productive of yellowish sputum at times but was not associated with any other symptoms, for example, dyspnoea, fever or haemoptysis. Initial chest X-ray was unrevealing. The severe cough persisted. A CT scan of the thorax in June of 2010 without contrast showed several hazy nodular opacities in the right upper lobe. Contrast was not given due to renal insufficiency. He was then treated with clarithromycin based on antibiotics sensitivity tests after sputum cultures grew *Mycobacterium chelonae/abscessus* complex. Unfortunately, drug interaction with cyclosporine resulting in elevation of serum creatine caused premature cessation of clarithromycin. He subsequently received oral azithromycin and intravenous meropenem, resulting in negative sputum smears although cultures remained positive. He was subsequently treated with tigecycline and linezolid. Shortly thereafter the patient revealed some improvement. In January of 2011, a surveillance CT of the thorax detected worsening of the nodular opacities shown previously in the right upper lobe now with cavitation formation. In addition, there were new lesions detected in left upper and lower lobes. An intratracheal obstructive lesion near the carina was noted (figure 1). Bronchoscopy detected papillomas in multiple areas including the trachea and the bronchus. Biopsy of the lesions revealed squamous cell carcinoma. Test for high-risk HPV was positive. Video-assisted thoracoscopic surgery with wedge resection confirmed lesion in the left lower lobe as squamous cell carcinoma.

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Figure 1 Bronchoscopic micrographs (A, B, C, H and I), CT (D and E), positron emission tomography (F and G) images showing polypoid growth in trachea near carina and lung cancer before (D, F, H and I,) and after (A–C, E and G) chemotherapy and erlotinib maintenance.

The patient does not have significant family history of cancer or leukaemia. However, he received a kidney transplant in July of 1998 after he developed end-stage renal disease from glomerulonephritis. He has since been on immunosuppressants, which consist of three-drug combination on average at a given time point. The immune suppressants include cyclosporine, prednisone, mycophenolate mofetil and tacrolimus. He is a non-smoker. He acknowledged exposure to second-hand smoke in a nightclub he owned. He denies any drug use or multiple sexual partners.

Patient was staged T4Nx, stage IV⁷ (The American Joint Committee on Cancer (AJCC) does not adequately address the tracheal primary staging; all primary tracheal malignancies are staged as stage IV as per AJCC criteria for lung carcinoma). He was treated with carboplatin and paclitaxel for four cycles starting August of 2011. Cough ceased after one cycle of chemotherapy. Restaging scan after four cycles showed complete response. He was since maintained on erlotinib. According to the latest

positron emission tomography (PET) performed on 7 August, 2012, he had no signs of residual papillomatosis although there was one area of carcinoma in situ on the left main stem bronchus which was present on initial diagnosis.

INVESTIGATIONS

CT of the thorax without contrast revealed intratracheal lesions near the carina (figure 1D). PET/CT showed fluorodeoxyglucose avid intraluminal growth and a right upper lobe lesion (figure 1F). Bronchoscopy with brushing and washing showed squamous cell carcinoma. A biopsy of papillomas in the trachea/carina region revealed squamous cell carcinoma (figure 2A,B). Immunostaining was positive for P16 (figure 2C). Genotyping of the HPV by ISH was positive for high-risk including genotype 16 (figure 2D) and 18 and negative for low-risk HPVs. The left lower lobe was positive for invasive squamous cell carcinoma (figure 2E) and stained positive for P16 (figure 2F).

Figure 2 H&E staining under low (A) and high (B) magnification showing papilloma and squamous cell histology with atypia, respectively. The specimen stained positive for P16 (C), human papilloma virus 16 (HPV16) DNA (in situ, D). The left lower lobe wedge biopsy was positive for invasive squamous cell carcinoma (E) and also stained positive for P16 (F).

Recent bronchoscopy after 1 year (figure 1A–C), CT (figure 1E) and PET (figure 1G) showed no gross disease.

DIFFERENTIAL DIAGNOSIS

- ▶ Pneumonia
- ▶ Bronchial alveolar carcinoma
- ▶ Squamous cell cancer of the trachea
- ▶ Non-small cell lung cancer
- ▶ Upper respiratory infection by atypical agents or virus

TREATMENT

He was treated with carboplatin and paclitaxel at area under the curve of 6 and 200 mg/m² for four cycles. Paclitaxel was started at a standard dosage at 200 mg/m². Dose was reduced 25% on cycle 3 and further down to 50% on cycle 4 due to grade 3 neuropathy. Erlotinib 150 mg once daily orally was started (19 November, 2011) as maintenance.

OUTCOME AND FOLLOW-UP

The patient finished four cycles of chemotherapy with carboplatin and paclitaxel (November 2011). A restaging scan showed only some residual activities. After initiation of erlotinib, the patient had subtle signs of the disease on a PET scan (last

August 2012). Cough was minimal. A repeat of bronchoscopy a year after diagnosis (August 2012) showed no signs of recurrence.

DISCUSSION

HPV infection is very common. Although the genotypes of HPV include up to 130, they can be classified into two types: the cutaneous type and the mucosal type. Initial infection may be cleared after interaction with the hosts. If persists, the virus may cause warts, papillomas or cancers depending on the genotypes. Whereas cutaneous type causes warts, mucosal infections including the anogenital and oral pharyngeal areas causes papillomas or cancer. Although benign papillomas are caused by the low-risk group HPV 6 and 11, HPV 16 and 18 usually result in cervical cancers or squamous cell cancer of the oral pharynx. HPV association with lung cancer is an unsettled issue; however,⁸ involvement of the lower airway by papillomas is reported only in a few cases.⁹ Known host factors¹⁰ affecting disease progression include tobacco smoking, coinfection with other sexually transmitted diseases such as HIV, hepatitis C or long-term immunosuppression in patients who are either on immunosuppressants for solid organ transplant or autoimmune diseases. Second-hand smoking can cause lung cancer. Second-hand smoking might

cause tracheal cancer as well. However, it is difficult to assess the role of second-hand smoking. Our patient is a transplant recipient who is immunosuppressed with clear evidence of HPV infection. Alternatively, his tracheal and bronchial malignancy might have been initiated by HPV infection and metastasis facilitated by immunosuppression.

Mainly caused by HPV 11, recurrent respiratory papillomatosis can be a challenge in diagnosis in early stage and in treatment. The diagnostic challenge in early stage results from its non-specific symptom whereas treatment has no effective curative approach at the moment. Surgical removal of lesion(s) is the main stay. Intralesional injections of antiviral agents such as interferon, cidofovir, indole-3-carbinol, retinoid are used as adjunctive therapy up to now.

Recently, research in the laboratory found that epidermal growth factor receptor (EGFR) is overexpressed through increased recycling from the membrane.^{11 12} As a result, there is increased signalling from the AKT–mitogen-activated protein kinase pathway. In addition, cyclo-oxygenase-2 expression is up-regulated resulting in increased prostaglandin-E2 expression in papillomas¹³. Based on these observations, combination use of erlotinib and celecoxib effectively suppressed growth of papillomas in a patient with refractory/resistant respiratory papillomatosis. This patient has failed surgical debulking plus intralesional injections, which are the current modality of treatments.^{14 15} A clinical trial using celecoxib to decrease the need for surgical debulking is recruiting patients (NCT00571701). In addition, systemic avastin or intralesional avastin in combination with angiolytic laser treatment seems to be effective.¹⁶

In a patient with squamous cell cancer transformation due to HPV 16 and 18 infections, the neoplasm seems to be chemotherapy sensitive as seen in our case. In addition, given the fact that EGFR is overexpressed in papillomas, and erlotinib maintenance is suitable for maintenance after first-line chemotherapy¹⁷ in non-small-cell lung cancer, erlotinib is a logical choice in these patients. Our experience seems to support such an idea. We all know chemotherapy in this case is not curative; it will be interesting to see how long the disease will remain dormant in such case. Close follow-up is needed in the future. Local therapy with ablation may be needed, should surveillance imaging reveal growth of the tracheal and bronchial lesion(s). Radiation therapy is a primary or adjunctive modality in the treatment for squamous cell cancer of the trachea.¹⁸

Learning points

- ▶ Respiratory papillomatosis is driven by the human papilloma virus (HPV). Although seen more often in children, it can also occur in adults. Risk factors for adults include multiple sex partners, oral sex and immunosuppression.
- ▶ Presenting with non-specific symptoms such as cough, hoarseness and airway obstruction symptoms, initial diagnosis might be difficult.
- ▶ High-risk HPV infection may be associated with malignant transformation.
- ▶ Treatment for benign papilloma is mainly by surgical removal in conjunction with intralesional injection of antiviral drug such as interferon and cidofovir.
- ▶ Recent reports of adjunctive therapies include antiangiogenic agents such as bevacizumab, or combination use of erlotinib and celecoxib.

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Contributors ZH was involved in manuscript writing, patient care and literature search. TD was involved in manuscript writing, patient care and micrograph. PB was involved in micrograph preparation and discussion. VP was involved in patient care, micrograph preparation and discussion.

Competing interests None.

Patient consent Obtained.

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