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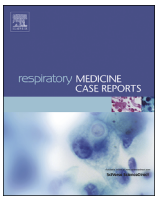

Case Report

Central airway squamous metaplasia following radiation therapy mimicking local tumour recurrence

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ABSTRACT

Radiation therapy can result in injury to the lung parenchyma and central airways; the latter is less well documented in the literature. Here, we describe a 65-year-old Caucasian male, who developed focal endobronchial nodules and right main bronchial stenosis suggesting tumour recurrence, 32 months following curative intent concurrent chemoradiation therapy for Stage 3B squamous cell carcinoma of the lung. Computed tomography and positron emission tomography results are detailed. Flexible bronchoscopy with bronchial biopsies revealed squamous metaplasia rather than malignant tumour recurrence, with ongoing observation planned.

1. Introduction

Radiation therapy can cause delayed injury to the lung parenchyma resulting in a spectrum of changes from radiation pneumonitis to radiation fibrosis [1]. Clinical manifestations range from asymptomatic, mild and rarely severe respiratory symptoms [1]. Central airway injury secondary to radiation therapy is less well documented, but can present as tracheobronchial squamous metaplasia, which may impair mucociliary clearance and rarely itself undergo neoplastic transformation [1–4]. Radiation exposure may also result in the formation of tracheobronchial strictures and stenosis [5,6]. We present the initial evaluation of a patient with suspected tumour recurrence who, after bronchoscopic biopsies, was found to have squamous metaplasia with the formation of a bronchial stricture; both outcomes are likely secondary to radiation therapy.

2. Case report

A 65-year-old Caucasian male, diagnosed with Stage 3B (T3 N3 M0) squamous cell carcinoma of the right upper lobe (RUL) three years earlier, was found on surveillance sequential Computed Tomography (CT) scans to have an interval increase in a residual right hilar mass and regional lymph nodes. He had been experiencing worsening exertional dyspnoea and intermittent haemoptysis over

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several months. He denied constitutional symptoms. Clinical examination revealed a mild-moderate bilateral expiratory wheeze and oxygen saturations within normal parameters (SpO2 = 96 % on room air).

32 months earlier, a thoracic cancer multi-disciplinary team had recommended curative intent concurrent chemoradiation therapy for a right hilar mass with a large right upper lobe endobronchial tumour deposit diagnosed at bronchoscopy. Treatment involved a 6-week daily course of radiation therapy at 66 Gy (Gy) in 33 fractions (2Gy per fraction, 10 fractions per fortnight) to the right lung and mediastinum (Fig. 1A and B). The chemotherapy regime included two cycles of cisplatin and etopophos, followed by maintenance 2-weekly durvalumab, for 12 months. The patient tolerated treatment generally well, with episodes of productive cough and pyrexia. Radiographic investigations showed a stable post treatment hilar mass and local nodes. There was no evidence of subacute radiation pneumonitis or fibrosis over 18 months of clinical follow up.

Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) at 21 and 27 months follow up showed stable findings, when compared with pre-chemoradiation scans (Fig. 1C). There was a decrease in the right hilar region activity (SUV_{max} 5.0 and 4.5, respectively from 9.0) and the right lower paratracheal node (SUV_{max} 3.5 and 3.7, respectively from 4.3). There was an increase in the uptake at the contralateral aortic arch node (SUVmax 5.9 and 6.4, respectively from 5.1), most likely due to reactive or inflammatory change. However, CT findings at 32-month review showed that the right suprahilar mass had increased in size to 70 × 30mm (previously 62 × 27mm) with narrowing of the RUL bronchus and right bronchus intermedius (Fig. 1D).

Local tumour recurrence was suspected and flexible bronchoscopy with ultrasound guided endobronchial biopsy was performed. Bronchoscopy prior to chemoradiation had shown an endobronchial RUL lesion with white nodules around the entrance of the RUL (Fig. 2A). The more recent bronchoscopy showed generalised hyperaemia and neovascularisation of the trachea (Fig. 2B) and RMB (Fig. 2C). The right bronchus intermedius was narrowed and slit-like from apparent extrinsic compression (Fig. 2C). The RUL also appeared to have a pinpoint orifice stricture (Fig. 2D). The distal bronchus intermedius, RML and RLL appeared normal. Two endobronchial nodules, one in the mid trachea and another in the bronchus intermedius (Fig. 2B and C), were thought to be tumour deposits and were biopsied.

However, the histopathology showed squamous metaplasia without overt dysplasia and altered stroma without obvious infiltration or keratinisation. Some fragments of mild chronic inflammation and fibrinous exudate were seen, without clear neoplastic change (Fig. 3). For persistent dyspnoea, insertion of a tracheobronchial silicon stent was attempted, but abandoned due to extreme friability of the bronchial mucosa during rigid bronchoscopy. Local balloon dilatation of the bronchus intermedius provided minimal symptomatic relief and an attempt at canulating and dilating the RUL stricture was unsuccessful. The patient continues undergoing 3 monthly clinical follow-ups with stable respiratory symptoms at the time of writing.

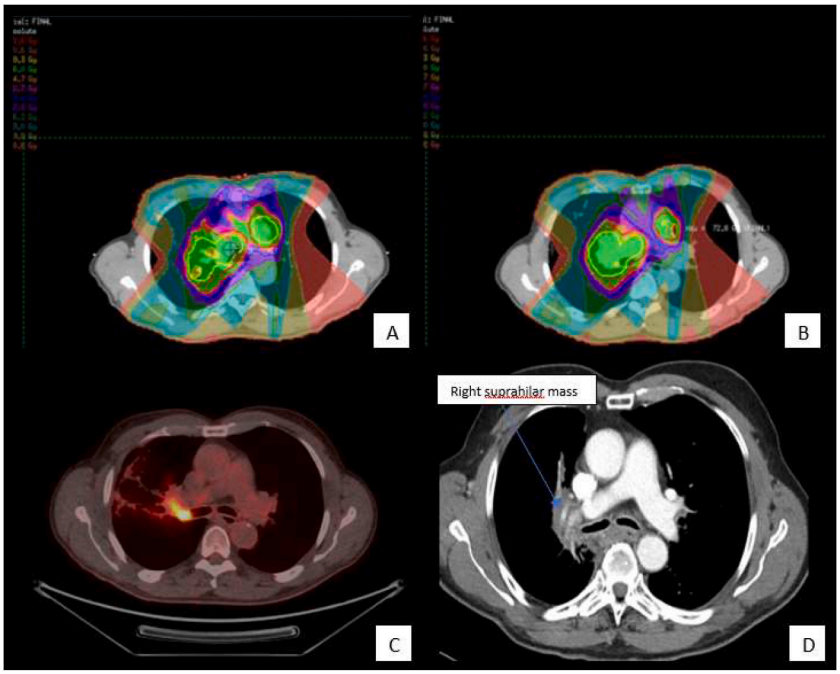

Fig. 1. Radiological Images. A & B: Radiotherapy plan at two levels showing the planning target volume (red), area receiving prescribed radiotherapy dose (green colourwash) and areas receiving lower doses (remaining colourwashes). C: Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scan pre chemoradiation therapy showing uptake in the right hilar region and right lower paratracheal and contralateral aortic arch nodes. D: Chest Computed Tomography showing the right suprahilar mass and lower paratracheal lymph node and subsequent narrowing of the lobe, 32 months post radiotherapy treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

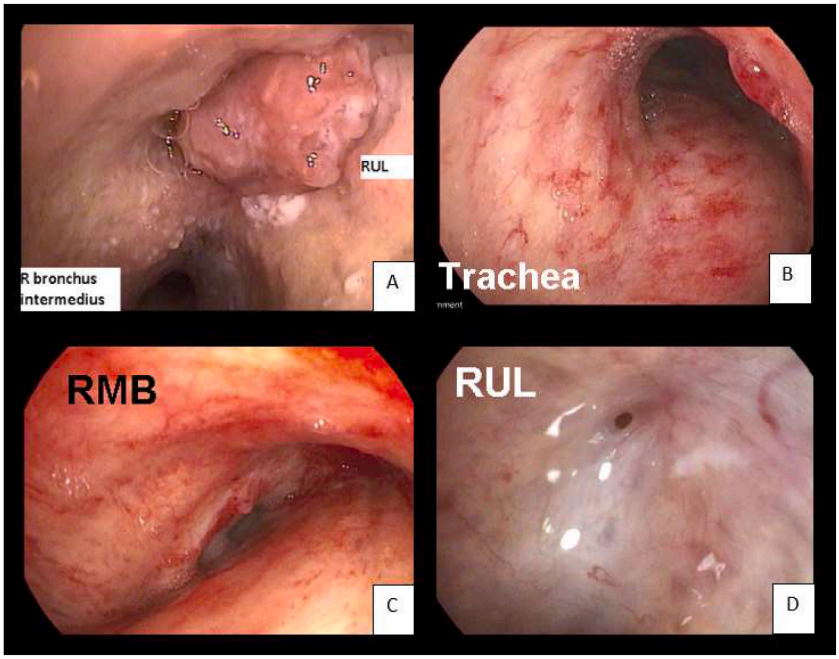

Fig. 2. Bronchoscopic image. A: Bronchoscopy prior to chemoradiation showing the RUL lesion and white nodules as viewed from the right main bronchus. Post radiation findings. B & C: Hyperaemia, neovascularisation of trachea and right main bronchus and a focal suspicious mucosal nodule. D: Pinpoint stricture of the Right Upper Lobe.

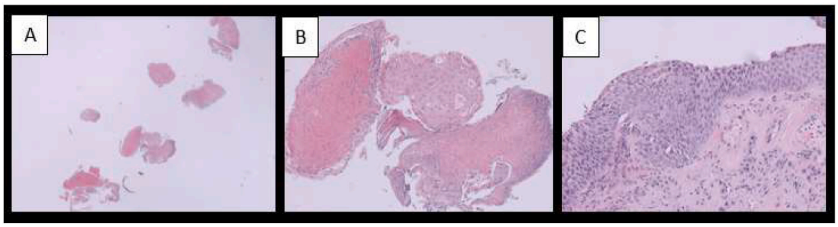

Fig. 3. Microscopic images. Biopsies of bronchus intermedius and tracheal nodules showing metaplastic squamous epithelium, with subepithelial stoma containing mild chronic inflammation and fibrinous exudate at A: low (2x objective), B: Intermediate (10×) and C: High (20x) magnification.

3. Discussion

Radiation therapy resulting in lung parenchymal injury is well documented [1]. Through the development of free radicals, ionising radiation can damage cell membranes and chromosomal DNA, contributing to epithelial cell dysfunction and death [1]. The lung's response to injury exists within a spectrum of acute to chronic changes [1]. Radiation pneumonitis describes focal or diffuse inflammation to lung parenchyma, occurring 4 weeks to 6 months following radiation exposure [1,7,8]. Patients may be asymptomatic or present with dyspnoea, cough, low-grade fever and/or chest discomfort. Symptoms may self-resolve, but more often require treatment with corticosteroids.

In more persistent cases, the lung architecture undergoes remodelling and permanent radiation fibrosis may result [1]. This can occur 6 months after treatment, and involves connective tissue deposition in place of normal lung tissue [1,7]. Patients may present with worsening dyspnoea, persistent dry cough or rarely with symptoms associated with cor pulmonale [1]. Radiation fibrosis is usually a clinical diagnosis based on history, signs and radiological findings and is often identified whilst investigating for post treatment symptoms, suspected infection or less commonly bronchiectasis or spontaneous pneumothoraces [1,7]. Risk factors associated with these complications include the dose and fractionation of radiation therapy, volume of lung irradiated, re-irradiation, the choice of chemotherapy agents and concurrent timing of chemotherapy with radiation, utilisation of immune therapy and abrupt corticosteroid withdrawal [1,8]. Management involves the consideration of these risk factors, using means such as dose-volume organ at risk constraints to guide optimal radiation dosing [9]. Whilst steroids may be effective for symptomatic radiation pneumonitis, these are ineffective for established fibrosis [1,8].

Central airway complications from radiation therapy are rarely reported in the literature. Squamous metaplasia of the tracheobronchial epithelium is a protective mechanism, involving the conversion of normal pseudostratified mucociliary epithelium to stratified squamous epithelium, and radiation exposure has been identified as a potential cause [1,2]. Miyamoto et al. (1987) reported two patients with pulmonary adenocarcinoma and squamous cell carcinoma respectively, who both developed squamous metaplasia fol-

lowing radiotherapy and anticancer medication [10]. The development of squamous metaplasia following radiation therapy for patients with squamous cell carcinoma of the mouth and oropharynx and breast carcinoma, have also been documented [11,12].

Interestingly, the pulmonary bronchi and bronchial epithelium are considered radioresistant [1]. Superimposed bacterial infection may lead to airway alteration, but its role in the development of squamous metaplasia is unclear [1]. COPD and smoking are contributing factors to the development of squamous metaplasia [3,13]. Worsening COPD severity, impaired mucociliary clearance, and neoplastic transition can result in patients with untreated squamous metaplasia [3,4,13]. Prognostic studies in this area are limited but smoking cessation is the only available management strategy for squamous metaplasia with proven efficacy [3,4]. Continual abstinence from smoking will be protective for our patient.

Radiation therapy and bronchial trauma may also result in bronchial strictures, as in our patient, which describes narrowing of the bronchial airways and tracheobronchial stenosis, potentially leading to post-obstructive pneumonia and symptomatic respiratory insufficiency [5–7]. Wang et al. (2020) showed the risk of developing bronchial strictures and atelectasis following radiation exposure is dose dependent [14]. Management options for strictures and stenoses include balloon dilatation and stent placement [5]. Cho et al. (2014) showed mean symptoms improvement of 61.9 ± 16 months with balloon dilatation and stent placement in patients with bronchial strictures following radiation therapy [6]. In the authors experience, stent insertion should be considered very cautiously as the risks of stent related complications in non-malignant conditions are high.

The need for further endobronchial treatments for our patient will need to be assessed with regular clinical surveillance reflecting a balance between symptoms and the risk of treatment related complications.

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Declaration of competing interest

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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