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An unusual recurrence of adenosquamous carcinoma of the lung

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Abstract
Adenosquamous carcinoma of the lung is an uncommon histological variant of non-small cell lung carcinoma (NSCLC) associated with a poorer prognosis than either adenocarcinoma or squamous cell carcinoma (SCC) histological subtypes. Most adenosquamous carcinomas of the lung present with advanced disease, often with the central nervous system as a common site of metastasis. We present a case of a patient with recurrent adenosquamous carcinoma who presents with multiple cerebral metastases, with two metastatic sites composed of separate distinct histological subtypes, one adenocarcinoma and one SCC. Interestingly, both metastatic deposits were also found to harbor an L858R epithelial growth factor receptor (EGFR) point mutation in exon 21. Upon progression after craniotomy and whole brain radiotherapy, the patient achieved a radiological response with the EGFR inhibitor, erlotinib.

1. Introduction

Lung cancer remains the most common cause of cancer death due to late presentation with advanced disease in the majority of cases. Mixed histology primary non-small cell lung cancer (NSCLC) is rare, although adenosquamous carcinoma represents the commonest subtype within this histological group, representing 0.4–4% of cases [1]. According to World Health Organisation's classification, adenosquamous carcinoma is defined as a carcinoma showing components of both adenocarcinoma and squamous cell carcinoma (SCC), with each component comprising at least 10% of the tumor [2]. Survival rates remain poor despite surgical resection in early stage disease compared to staged-matched NSCLC cases with a high preponderance for cerebral metastasis as a site of distant recurrence [3]. The incidence of separate histological phenotype in cerebral metastasis of adenosquamous carcinoma has not been previously reported and we describe a case of this unusual pattern of recurrence.

A 65 year old male initially presented with chest pain in September 2010. He had a remote smoking history of 4 pack

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years of smoking and had quit 43 years earlier. Investigation with a chest x-ray revealed 58 mm left upper lobe mass. Endobronchial biopsy demonstrated NSCLC. Complete staging with computer tomography (CT) and 18-Fludeoxyglucose Positron Emission Tomography (FDG-PET) revealed no nodal or distant metastatic disease and he proceeded to definitive left upper lobectomy. Thorough histopathological examination revealed an adenosquamous variant of NSCLC with the adenocarcinoma component positive for thyroid transcription factor 1 (TTF-1) and CK7 representing 30% of the total specimen and the SCC component positive for p63 and CK5/6 and negative for TTF1 and CK7 representing the remaining 70% of the tumour (Figure 1). The tumour measured 60 mm and invaded the visceral pleura with extensive lymphovascular invasion. There were peribronchial and left hilar lymph node involvement with metastatic disease resulting in a pathological stage of pT2bN1M0.

Post-operatively, he received four courses of adjuvant cisplatin (50 mg/m^2 day 1 and 8) and vinorelbine (25 mg/m^2 day 1, 8 and 15) every 4 weeks completed by March 2011. Ten months later (January 2012) he was found to have a left paratracheal and aorto-pulmonary nodal recurrence on routine follow-up CT imaging. This was confirmed with a transbronchial nodal biopsy with histological examination demonstrating recurrent SCC. FDG-PET did not reveal any extrathoracic metastasis. Subsequent imaging of the brain with CT and magnetic resonance imaging (MRI) scan (Figure 2) demonstrated three cerebral metastases, two in the left frontal lobe (26×43 mm and 19×14 mm) with 8 mm midline shift and one in right frontal lobe (15×7 mm) complicated by new onset of generalised seizures requiring levetiracetum.

The patient subsequently then underwent a craniotomy and resection of the two left frontal lobe metastases. Thorough histological assessment of both metastases interestingly demonstrated two distinct histological subtypes, one adenocarcinoma and the other SCC, both with distinct cytokeratin profiles consistent with the differing histological morphologies. Furthermore, the both metastatic deposits were found to harbor a L858R epithelial growth factor receptor (EGFR) point mutation in exon 21. He received post-operative whole brain radiation to a dose of 30 Gy in ten fractions [4,5].

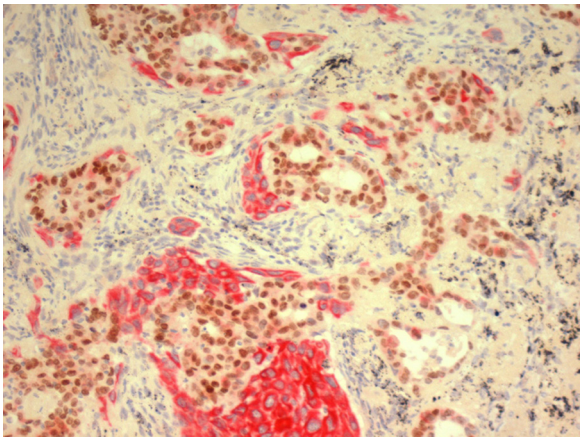

Figure 1 Histology of the adenosquamous carcinoma of the lung. The brown chromogen stains thyroid transcription factor 1 (TTF-1) representing the adenocarcinoma component. The red chromogen stains CK5/6 representing the squamous cell carcinoma component.

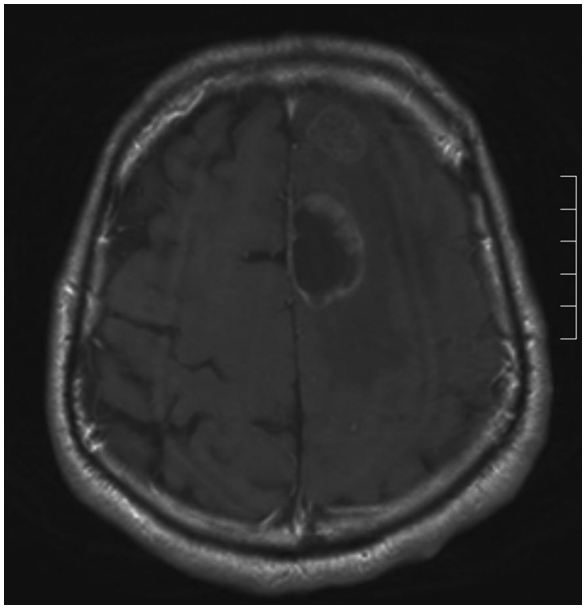

Figure 2 Magnetic resonance imaging of the brain (T1 weighted images post gadolinium contrast) demonstrating two cerebral metastases. The adenocarcinoma metastasis is the solid anterior lesion and the squamous metastasis the posterior cystic lesion.

Unfortunately, subsequent imaging after completion of whole brain radiotherapy revealed further progression of the contralateral right frontal lobe lesion which now measured 32×22 mm (compared to 15×7 mm previously) and evidence of residual disease in the surgical frontal lobe cavity. Erlotinib was commenced in an attempt to adequately treat both the systemic and CNS disease based on data from various studies [6-9]. Erlotinib was generally well tolerated with grade II acneform rash and diarrhoea requiring the addition of doxycyline 100 mg bd and loperamide for management of these adverse effects with good effect. Follow up imaging with whole body CT scan and MRI of the brain initially demonstrated both a response to his intracerebral and mediastinal nodal disease without evidence of new distant metastasis.

Due to subsequent slow progression of the CNS metastases, the patient subsequently underwent a redo-craniotomy for the disease in the left frontal lobe followed by further whole brain radiotherapy to an additional dose of 20 Gy in 10 fractions. Repeat mutational analysis was not performed and the patient remained on erlotinib for 24 months with follow up imaging demonstrating further minor progression of his left frontal lobe disease, stable disease in the mediastinal nodal disease and the appearance of asymptomatic bony metastases in lumbar vertebra 3 and 4. After further clinical and radiological deterioration, and increase frequency of complex partial seizure despite escalating doses of levetiracetum, the patient died in April 2014, 27 months after the initial development of multiple cerebral metastases.