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Case Report

# Pseudoprogression following neoadjuvant chemoimmunotherapy for lung squamous cell carcinoma mimicking pulmonary metastatic disease on computed tomography: A case report and review of the literature ☆,☆☆

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ABSTRACT

Pseudoprogression of malignancy in patients treated with systemic immunotherapy is a well- recognised phenomenon and has also been seen in patients treated with combined chemoimmunotherapy. Neoadjuvant chemoimmunotherapy prior to surgery is a relatively new treatment strategy for the management of many malignancies. We report the case of a patient who was suspected to have primary lung squamous cell carcinoma progression following neoadjuvant chemoimmunotherapy. Tissue histopathology from biopsies demonstrated granulomatous sarcoid-like inflammation rather than progression or metastatic dis-

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ease. The patient proceeded to have successful surgical clearance of residual tumour. Significantly, failure to suspect granulomatous reactions and pseudoprogression has profound influence on the trajectory of patient care, such as, the potential for patients to miss out on curative surgery. In this case report and review of the literature, we evaluate the role of pseudoprogression and the need for radiologists to be aware of this phenomenon so that they do not mistakenly report new metastases and derail the treatment paradigm for patients with curable malignant conditions.



## Introduction

Neoadjuvant chemoimmunotherapy followed by surgery is a new treatment paradigm for locally advanced non-small cell lung cancer (NSCLC) [1]. With the advent of this novel approach, a phenomenon known as pseudoprogression has become increasingly recognized [2,3]. Pseudoprogression is commonly defined as an increase in primary tumor size, or the development of new lesions, followed by shrinkage of the tumor or achievement of stable disease during the course of immunotherapy [4]. One manifestation of pseudoprogression in the context of primary lung malignancy is the development of granulomatous sarcoid-like changes [5,6]. These reactions are rare, with an estimated incidence of 1.3% to 3.2% based on observational data [7–9]. These findings are often picked up on repeat radiological assessment, such as through computer tomography (CT) and positron emission tomography (PET) imaging. Importantly, radiologic pseudoprogression and manifestations such as granulomatous reactions are great mimickers of malignant progression and metastatic disease. For radiologists, it is important to recognize these changes in the context of novel systemic chemoimmunotherapy regimens as failure to do so, or inappropriate reporting of new metastatic disease or progression of primary malignancy, can derail definitive curative treatment for the patient. Furthermore, lack of timely recognition of pseudoprogression can also lead to delays in definitive decision making due further staging initiatives with radiology, biopsy and multidisciplinary discussion. We report a case of a 47-year-old man with primary non-small cell lung cancer who develops pseudoprogression secondary to granulomatous changes in the context of neoadjuvant chemoimmunotherapy. Through this case, we further discuss the challenges with appreciating this condition and insights into decision making for such cases.

## Case report

A 47-year-old man presented an incidental finding of right upper lobe lesion on CT of the chest. Following investigations, a diagnosis of clinical stage IIIA (cT4, cN1, cM0) pulmonary squamous cell carcinoma (SCC) was made (Fig. 1). Following multidisciplinary discussion, he proceeded to neoadjuvant chemoimmunotherapy with three cycles of nivolumab, carboplatin and paclitaxel for three cycles followed by surgery with curative-intent. A [$^{18}$F] fluorodeoxyglucose (FDG)-PET/CT scan following neoadjuvant chemotherapy for restaging demonstrated reduction in size of the primary tumor with marked reduction in avidity (Figs. 2, 3A and B). However, numerous new non-avid nodules were found in both lungs, suspicious for lung metastases (Figs. 4A-D).

Given the mixed findings, multidisciplinary team discussion recommended biopsy of one of the new lesions. The patient underwent right uniportal video-assisted thoracoscopic surgery (VATS) and middle lobe wedge resection. Histopathology confirmed non-necrotising granulomatous inflammation with no evidence of malignancy. Subsequently, the patient underwent right pneumonectomy and lymph node dissection. Histopathology revealed poorly differentiated SCC of the right upper lobe, 11 mm in size alongside prominent sarcoidosis-like non-necrotising granulomatous reactions of the lymph nodes and throughout lung parenchyma (ypT1b, N0, M0). He recovered without complications and is currently recurrence free at 6 months.

## Discussion and conclusions

Systemic chemoimmunotherapy is a cornerstone in the management of non-small cell lung cancer [10]. Pseudoprogression is an increasing recognized phenomenon associated with immunotherapy. Due to the resemblance of pseudoprogression to metastatic disease or malignant disease progression, such as with granulomatous reactions in this case, these changes pose a diagnostic challenge. Given the significance of this on the trajectory of patient care, it is important for clinicians to become aware of such changes to allow patients the best opportunity at definitive curative intent treatment. Imaging plays a pivotal role in the assessment of treatment response and disease progression in NSCLC [11]. However, distinguishing true disease progression from pseudoprogression remains challenging. The use of CT and FDG-PET is widely utilized to monitor and stage pulmonary malignancies [12]. The value of restaging in evaluation of response to chemotherapy is controversial, due to the poor specificity and sensitivity in delineating malignancy from these granulomatous changes [13]. Unfortunately, there is currently no reliable method to distinguish pseudoprogression to disease progression or metastatic disease. The diagnosis of pseudoprogression on FDG-PET therefore relies on clinical suspicion by the treating team and radiologist, particularly if there is evidence of apparent disease progression (increase in size and FDG-avidity of pre-existing lesions or increase in num-

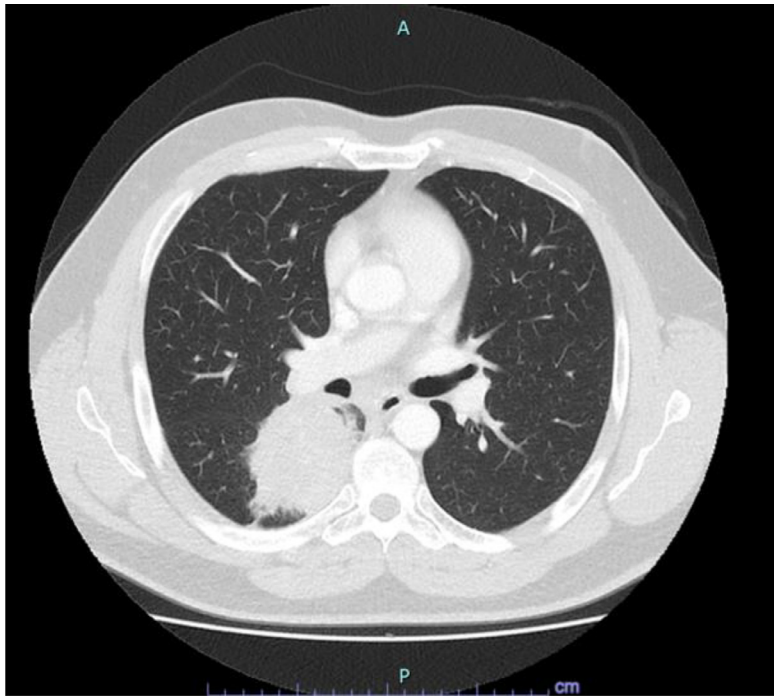


**Fig. 1 – Postcontrast computed tomography (CT) of the chest image of the right upper lobe mass sized 64 x 68 x 67 mm.**

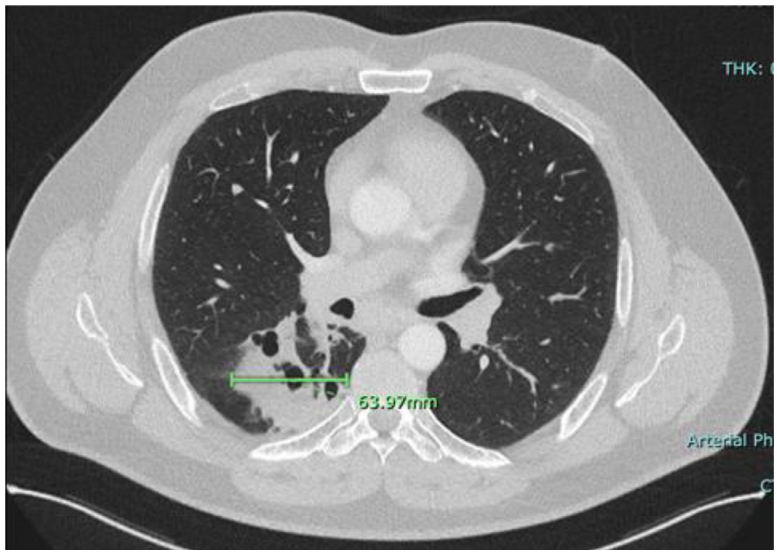


**Fig. 2 – Postcontrast CT of the chest image of the right upper lobe mass sized 64 x 64 x 67 mm with evidence of reduced solid component post neoadjuvant chemoimmunotherapy.**

ber of FDG-avid lesions) within 12 weeks of immunotherapy commencement [14]. Due to this lack of specifity, false-positive radiotracer uptake has been reported for granulomatous nodes in the context of malignancy re-staging [13]. The significance of this finding has implications for the patient and the clinicians involved. Firstly, these false-positive findings, and the assumption of failed metabolic response, significantly impairs appropriate prognostication of pulmonary malignancies, which have been shown to exhibit favorable outcomes when metabolic response is demonstrated on PET [15]. Misleading diagnoses that may result from these findings can lead to significant consequences for the patient including lack of definitive surgical management, ongoing unnecessary systemic therapies and therefore adverse side-effects of these approaches. Moreover, the psychological impact of false-positive diagnoses on the patient must also be considered.

Awareness of the possibility of pseudoprogression and its radiological manifestations is crucial for radiologists and oncologists involved in the management of NSCLC patients.

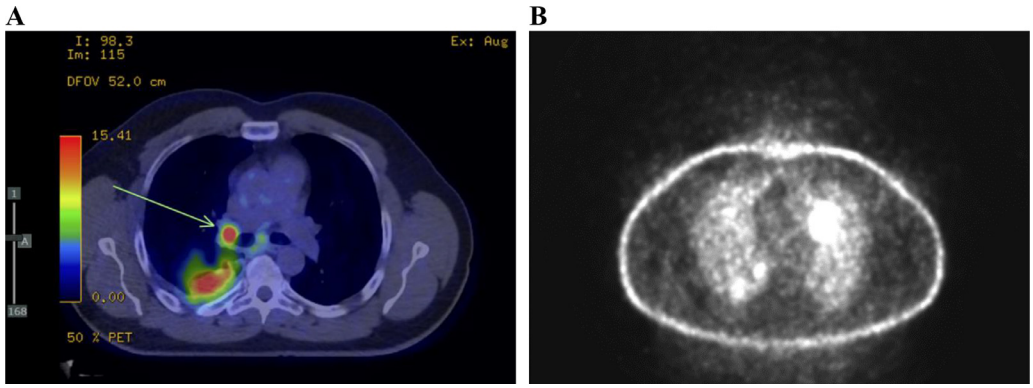


**Fig. 3 – (A) FDG-PET/CT of the chest prior to commencement of chemoimmunotherapy demonstrating moderate focal uptake in the superior segment of right lower lobe medially. (B) FDG-PET/CT of the chest (nonattenuation-corrected) post chemoimmunotherapy demonstrating marked reduction in avidity and molecular volume of the right lower lobe primary lesion.**

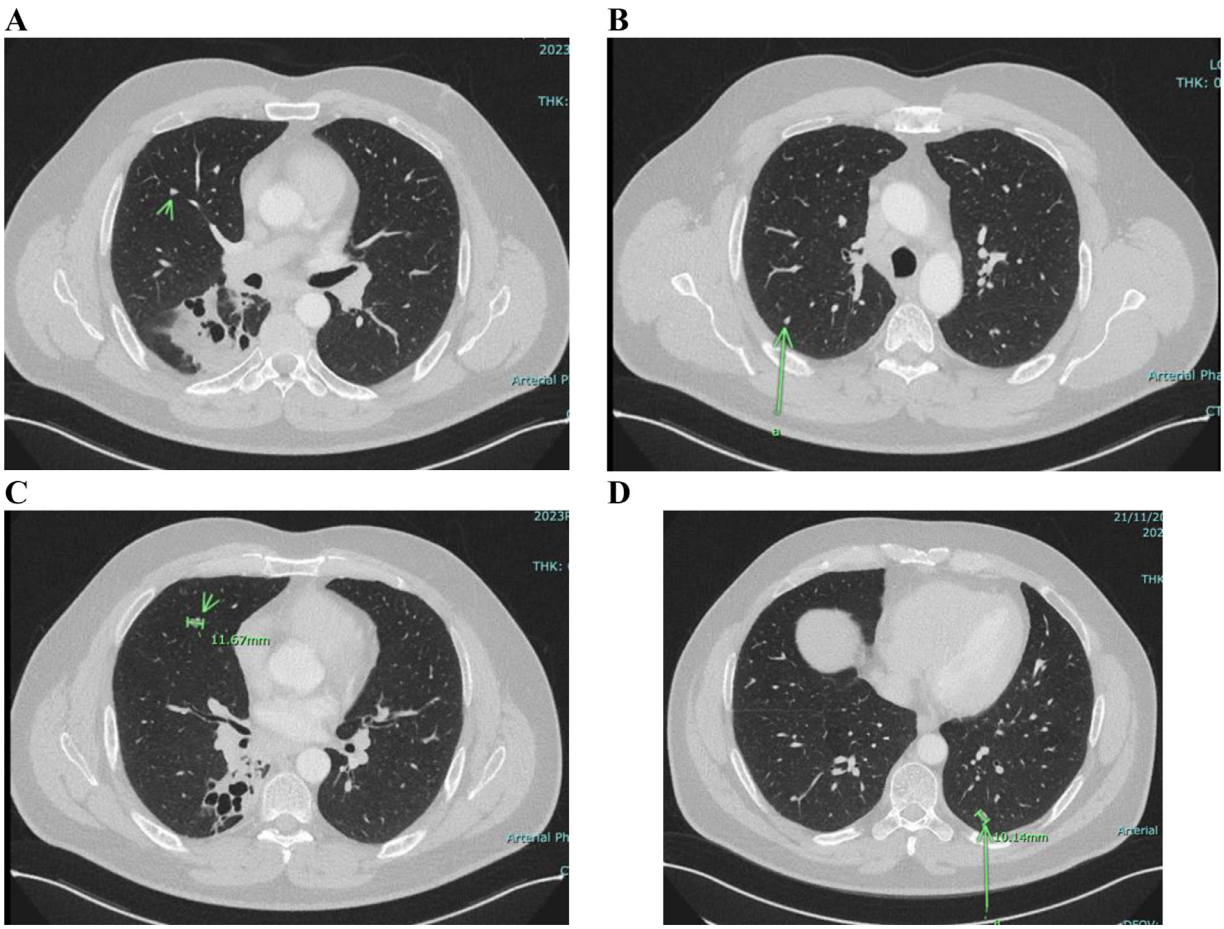


**Fig. 4 – (A-D) Postcontrast CT of the chest images of numerous lung nodules increased in size presumed to represent lung metastases post neoadjuvant chemoimmunotherapy.**

Histopathological confirmation through biopsy or close clinical and radiological follow-up is essential in cases where pseudoprogression is suspected. This ensures that appropriate management decisions are made, avoiding unnecessary treatment escalation or delay in initiating potentially beneficial therapies.

## Patient consent

The patient provided informed consent that was written and signed for generation and publication of this manuscript using their de-identified medical information.

## Data availability statement

Data can be requested from corresponding author when required. All relevant data has been provided in the generation of this manuscript which is intended for open access publication.

## Ethics approval and consent to participate

The case report generation process was discussed with our local ethics and governance team. No formal ethics approval was required following the discussions and therefore was waived. The patient provided written consent for the de-identification and use of their medical information and data for the generation and publication of this case report.

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