

## CASE BASED DISCUSSION

# Pulmonary aspergillosis: an alternative diagnosis to lung cancer after positive [<sup>18</sup>F]FDG positron emission tomography

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## ABSTRACT

[<sup>18</sup>F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) scans have significantly improved the diagnosis and staging of lung cancer, but false-positive scans are known to occur due to inflammatory and infectious diseases. Recognition of the conditions leading to false-positive scans is important. Single or multiple pulmonary nodules, with or without cavitation, are classical findings in acute and chronic pulmonary aspergillosis. Clinical features of pulmonary aspergillosis are very similar to those of lung cancer. This report highlights pulmonary aspergillosis as an alternative diagnosis to lung cancer in patients with positive [<sup>18</sup>F]FDG PET scans and the need to strive for presurgical histological diagnosis.

## INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths for both men and women in the UK. Early diagnosis and treatment can improve morbidity and mortality. The introduction of positive emission tomography (PET) has led to improved diagnosis, staging and treatment evaluation for lung cancer. PET sensitivity to detect malignant pulmonary cells is ~96%.<sup>1</sup> However, it is now recognised that a number of granulomatous, infectious and inflammatory conditions can also demonstrate increased [<sup>18</sup>F]fluorodeoxyglucose (FDG) uptake.<sup>2</sup> These false positives lead to a lower PET specificity than sensitivity, at ~78%.<sup>1</sup> Awareness of the conditions that can mimic lung cancer on PET scan is vital, not only to allow early exclusion of lung cancer but also to aid the rapid detection and treatment of these conditions. The importance of *Aspergillus* as a lung pathogen and allergen is increasing, and treatment options are improving. This report highlights pulmonary aspergillosis as an important cause of PET-positive scans and the continued need for presurgical histological diagnosis.

## CASE REPORTS

### Case 1

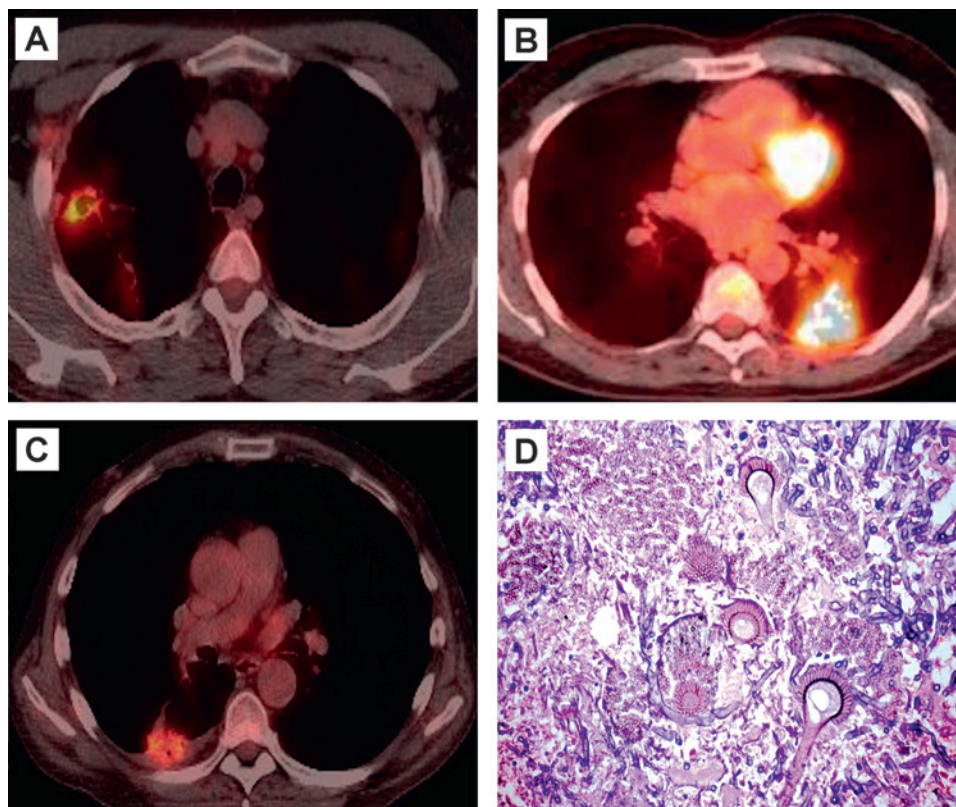
This 54-year-old gentleman, ex-smoker, presented with a 2 month history of progressive right-sided chest pain, cough and breathlessness. His chest radiograph (CXR) showed abnormal shadowing in the right upper lobe (RUL), and CT scan demonstrated a cavitating lesion in the RUL with surrounding fibrosis extending to the pleura. Lung

function showed a forced expiratory volume in 1 s (FEV<sub>1</sub>) of 58% predicted and his performance status was 1. He subsequently had a bronchoscopy that showed epithelial inflammation. Cytology of the bronchial wash was negative for malignant cells and culture was negative. PET/CT was performed to further characterise and stage the mass seen on CT. It confirmed a 2 cm cavitating mass in the RUL with avid FDG uptake (maximum standardised uptake value (SUVmax) 7.2 g/ml) and intermediate uptake in the surrounding fibrotic area (figure 1A). Additionally, there was intermediate uptake in a right subclavian lymph node (SUVmax 3.1 g/ml). He went on to have a thoracotomy with wedge resection of the RUL for presumed malignancy. Histology demonstrated a cavity lined by granulation tissue and filled with necrotic material and septate fungal hyphae consistent with *Aspergillus* (figure 1D). There was no evidence of malignancy. Serological blood tests were performed which demonstrated strongly positive *Aspergillus* immunoglobulin G (IgG) antibodies, supporting a diagnosis of chronic pulmonary aspergillosis (CPA). He was commenced on itraconazole.

### Case 2

This 52-year-old gentleman presented with a 3 month history of non-productive cough, wheeze, breathlessness and left upper chest pain. He was a non-smoker with known mild asthma. Despite antibiotics and an increase in his asthma treatment he continued to deteriorate. Spirometry showed a 10% fall in his baseline FEV<sub>1</sub> of 86% predicted. Routine blood tests showed an eosinophilia of 2.95×10<sup>6</sup>/l but no other abnormalities. CXR showed a large mass in the left upper lobe (LUL). CT scan confirmed a complex 5 cm mass in the LUL with proximal bronchiectatic airways. The soft tissue mass was felt to be highly suspicious for malignancy. Thick mucus was seen at bronchoscopy throughout the LUL, histology of which showed inflammatory cells but no malignant cells, and culture was negative. PET/CT showed the 5 cm mass to have avid FDG uptake (SUVmax 8.3 g/ml) and there were multiple FDG-avid mediastinal lymph nodes (figure 1B). PET staging was of a T4 N2 M0 pulmonary malignancy. To obtain a definitive histological diagnosis, a thoracotomy with LUL wedge resection was performed. However, histology did not show any malignant cells but foci of necrosis surrounded by histiocytes. Within the

**Figure 1** Positron emission tomography (PET) and histology images. (A) PET/CT of Case 1 showing a 2 cm cavitating mass in the right upper lobe with high fluorodeoxyglucose (FDG) uptake plus an area of fibrosis surrounding the mass extending to the pleura with intermediate FDG uptake—diagnosis chronic pulmonary aspergillosis (B) PET/CT scan of Case 2 showing a 5 cm mass in the left upper lobe abutting the pleura plus multiple lymph nodes; all areas had high FDG uptake—diagnosis allergic bronchopulmonary aspergillosis (C) PET/CT of Case 3 showing a 3 cm mass in the right lower lobe abutting the pleura with intermediate FDG uptake—diagnosis subacute invasive aspergillosis (D) Histological specimen from Case 1 showing necrotic material and septate fungal hyphae with conidial heads consistent with *Aspergillus*.



areas of necrosis, Grocott stain demonstrated multiple hyphal fragments consistent with *Aspergillus*. Serological blood tests confirmed a diagnosis of allergic bronchopulmonary aspergillosis: total IgE 8045 kIU/l, *Aspergillus*-specific IgE 36.7 kUa/l, *Aspergillus*-specific IgG >200 mg/l. After 1 year of itraconazole there was complete resolution of the mass on CT.

### Case 3

This 55-year-old gentleman, ex-smoker, presented with cough, breathlessness and weight loss over 3 months. CXR showed

a left lower lobe mass and this was confirmed on CT scan as a 3 cm solid mass abutting the pleural surface, highly suspicious for malignancy. There was no lymphadenopathy. Routine bloods were normal and spirometry showed an FEV<sub>1</sub> of 67% predicted. Staging PET/CT demonstrated the left lower lobe mass to have intermediate FDG uptake (SUV<sub>max</sub> 4.0 g/ml) and confirmed no FDG-avid lymph nodes (figure 1C). He went on to have an open wedge resection with planned pneumonectomy if frozen section was positive for malignancy. Histology from the biopsy did not demonstrate any malignant cells but a large area

**Table 1** Patient investigations and treatment

	SUVmax (g/ml)	Operation	Histology	<i>Aspergillus</i> IgG (mg/l)	Precipitin titre	Total IgE (kIU/l)	<i>Aspergillus</i> IgE (kUa/l)	Diagnosis	Treatment
Case 1	7.2	Wedge resection	Septate fungal hyphae and conidial heads	78	1/2	42	0.5	CPA	Itraconazole
Case 2	8.3	Wedge resection	Hyphal fragments	>200	1/2	8045	36.7	ABPA	Itraconazole
Case 3	4.0	Wedge resection	Fungal hyphae involving adjacent blood vessels	28	1/2	1100	40.5	Subacute IA	Voriconazole
Case 4	3.5	CT-guided biopsy	Fungal hyphae admixed with spores	82	1/2	90	<0.4	CPA	Posaconazole
Case 5	2.6	Wedge resection	Branching fungal hyphae	66	1/16	570	8.0	CPA	Itraconazole
Case 6	3.9	CT-guided biopsy	Branching fungal hyphae	94	1/4	140	<0.4	CPA	Itraconazole
Case 7	2.2	Wedge resection	Fungal hyphae admixed with spores	56	Neat	1000	14.9	CPA	Itraconazole
Case 8	7.9	Wedge resection	Branching fungal hyphae	50	Neat	73	<0.4	CPA	Voriconazole
Case 9	9.0	CT-guided biopsy	Branching fungal hyphae	76	1/64	62	<0.4	CPA	Itraconazole
Case 10	2.9	Lobectomy	Aspergilloma	—	1/2	61	<0.4	Simple aspergilloma	No antifungals

IgE and IgG determinations were performed by ImmunoCAP assay (Phadia) and precipitins by immunoelectrophoresis (using antigens from Microgen Bioproducts, Surrey, UK). ABPA, allergic bronchopulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; Ig, immunoglobulin; SUV<sub>max</sub>, maximum standardised uptake value.

of necrosis surrounded by granulomatous inflammation. Within the necrotic material there were numerous fungal hyphae and conidial heads consistent with *Aspergillus*. Adjacent blood vessels and bronchi demonstrated hyphal invasion in keeping with a diagnosis of subacute invasive aspergillosis. *Aspergillus* serology was positive: total IgE 1100 kIU/l, *Aspergillus*-specific IgE 40.5 kUa/l; and positive for *Aspergillus nidulans* precipitins. He made a full recovery on voriconazole.

## DISCUSSION

These three cases highlight the wide spectrum of *Aspergillus*-related pulmonary diseases that can present with symptoms, signs and radiological features overlapping those of lung cancer. Between 2008 and 2010 a further six cases of CPA and one simple aspergilloma, in patients presumed to be immunocompetent, have been referred from within Greater Manchester to our centre (table 1). These 10 cases all presented with a history, symptoms and CT features suspicious of lung cancer. PET scans, done for staging and treatment planning, were positive.

CPA is a progressive and destructive pulmonary infection. It is associated with underlying pulmonary conditions that lead to formation of cavities, bullae or scarring in the lungs, such as prior mycobacterial infection, emphysema and sarcoidosis.<sup>3</sup> The prevalence of CPA is not known and will depend on the prevalence of underlying pulmonary diseases, but is estimated to be 3 million people worldwide (DWD, unpublished data). The reasons why some patients develop pulmonary aspergillosis while others do not are not understood. It is most likely to relate to subtle immune or pulmonary defence defects such as mannose-binding lectin deficiency or immune dysregulation such as T helper 2 (Th2) cell axis predominance.<sup>4</sup> Symptoms of CPA are non-specific and include cough, breathlessness, weight loss and fevers. A frequent complication is haemoptysis, which can be life threatening. Diagnosis is based on the presence of symptoms and radiological features, and the demonstration of specific *Aspergillus* IgG antibodies or positive respiratory cultures.<sup>4</sup> IgG antibodies can be detected using the ImmunoCAP method (Phadia, Uppsala, Sweden) or by the detection of precipitating antibodies. The ImmunoCAP method is a fast, automated fluorescent immunoassay that has replaced tests for precipitins in many UK laboratories. A level of >40 mg/l is considered indicative of aspergillosis. Cut-off levels have not been examined or determined for the different forms of pulmonary aspergillosis, and population prevalence is not known. The sensitivity of culture of *Aspergillus* from respiratory secretions is poor, but real-time PCR will significantly improve this.<sup>5</sup> Nevertheless, neither serology nor detection of *Aspergillus* in pulmonary secretions can rule out a diagnosis of lung cancer. The prevalence of concomitant positive *Aspergillus* antibodies or *Aspergillus* cultures in lung cancer is not known. Many patients with lung cancer also have emphysema, one of the most common underlying conditions for pulmonary aspergillosis. Both lung cancer and aspergillosis may occur simultaneously, which is particularly problematic in those with multiple lesions.

As seen in case 2, allergic bronchopulmonary aspergillosis, unlike CPA and invasive aspergillosis, often has diagnostic features in the history or baseline investigations which help to distinguish it from malignancy. However, it remains of utmost importance not to miss a diagnosis of lung cancer and therefore histological diagnosis must always be obtained when radiological features are suggestive of malignancy.

This report highlights the importance of how this histological diagnosis is reached. In recent years non-surgical methods of tissue diagnosis and staging have developed significantly, including the use of CT-guided biopsy, endobronchial ultrasound and medical thoracoscopy. Seven of the 10 patients in this report had open surgical biopsies, while three had CT-guided biopsy. All cases were amenable and medically fit to have CT-guided biopsy. The decision to proceed directly to open surgical biopsy often depends on the assumed likelihood of malignancy and the ability to achieve complete surgical resection of early, non-metastatic malignancies. It can therefore often be difficult to achieve the balance of attaining early resection of malignancy and preventing unnecessary surgery in cases that prove not to be malignant. Surgery can have significant complications and morbidity including infection and postoperative pain. CT-guided biopsy, where available and appropriate, can allow histological detection of *Aspergillus* and, if coupled with serology or real-time PCR to identify fungi in respiratory secretions, can support a diagnosis of pulmonary aspergillosis over malignancy. Nevertheless, where there remains a clinical suspicion of concomitant malignancy, surgery may still be required.

In summary, all forms of pulmonary aspergillosis can lead to symptoms and radiological signs similar to lung cancer. The prevalence of treatment-responsive CPA is rising significantly, hence the need to increase awareness of this condition. It is vital not to miss a diagnosis of lung cancer, but non-surgical biopsies, together with *Aspergillus* serology, can help identify one cause of false-positive PET scans.

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