Case Report

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Lung adenocarcinoma and sequential antineutrophil cytoplasmic antibody-associated vasculitis: a case report

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Abstract

The relationship between antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and lung cancer remains unclear. A 66-year-old man presented with pulmonary nodules. Histological examination of a specimen from computed tomography-guided percutaneous transthoracic biopsy revealed adenocarcinoma. The patient was treated using cryoablation and systemic chemotherapy. Sixteen months later, the patient presented with fever, nasal inflammation, recurrent lung lesions, elevated serum creatinine levels, and high levels of ANCA. Histological examination of a specimen from ultrasound-guided percutaneous renal biopsy revealed pauci-immune necrotizing crescentic glomerulonephritis. The patient responded to treatment, but granulomatosis with polyangiitis recurred and he later died. This case highlights the possibility of sequential AAV with lung cancer. Although this is relatively rare, further research is needed to better understand the association or pathophysiological link between lung cancer and AAV.

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Introduction

The association between antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and lung cancer remains unclear. Some studies have suggested an association or causative link between cancer and AAV,[1–3] because AAV can occur in conjunction with other autoimmune diseases and is treated using immunosuppressive therapy,[1,3–5] and cancer may be a potential risk factor for AAV.[2]

There are few reported cases of lung cancer diagnosed before, concurrently, or after AAV.[1,2] Here, we present the case of a patient with lung adenocarcinoma who was treated using cryoablation and chemotherapy. The patient subsequently developed granulomatosis with polyangiitis (GPA) that presented as fever, nasal inflammation, and recurrent lung lesions, along with elevated levels of ANCAs and serum creatinine.

Case presentation

This study was approved by the Ethics Committee of The Sixth Medical Center of PLA General Hospital (approval no. HJQX2013-6-1). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The patient consented to treatment before the initiation of any kind of treatment or procedure. Written informed consent to participate in this study and to publish images or data included in this article was obtained from the patient.

In 2011, a 66-year-old man presented with pulmonary nodules. After 2 years of active monitoring, the pulmonary nodules began to increase in size. The patient developed a mild cough with a small amount of bloody sputum. He had smoked 1.5 packs of cigarettes a day for the past 30 years and denied any family history of cancer or autoimmune diseases. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed metabolically active lesions with intense FDG uptake in the bilateral upper lung lobes (Figure 1). Computed tomography (CT)-guided percutaneous transthoracic biopsy was performed on the mass in the left upper lobe (Figure 2A). Pathological testing identified the mass as stage T2aN3M1a (grade IV) adenocarcinoma (Figure 2B) with no genomic mutations. Laboratory testing showed a C-reactive protein level of 5.1 mg/L (reference range: 0–8 mg/L) and a serum creatinine level of 94 μmol/L (reference range: 62–115 μmol/L); a urinalysis was normal. In April 2013, the patient underwent cryoablation of the bilateral upper lobe lesions (Figure 3A a and b). In May and September 2013, the patient underwent six cycles of paclitaxel and cisplatin chemotherapy.

In May 2014, the patient was referred to our center. Thoracic CT showed that the lesion in the left upper lobe had not markedly decreased in size (Figure 3B a and b). A third round of cryoablation was

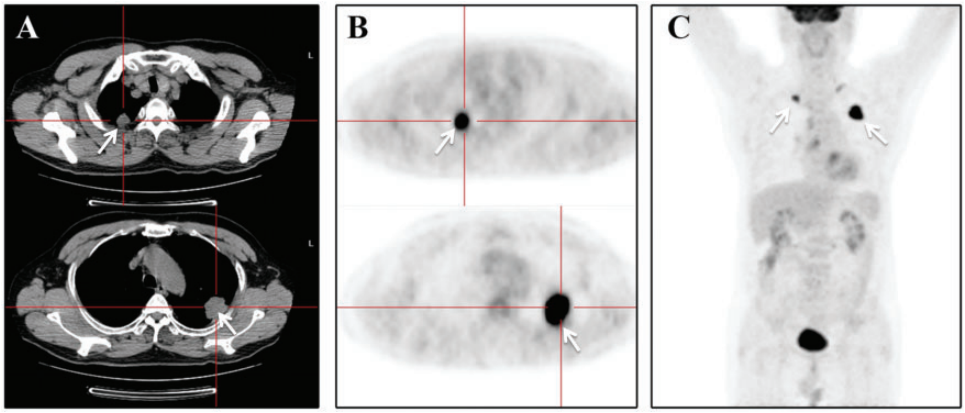

Figure 1. Positron emission tomography (PET)/computed tomography (CT) revealed bilateral hypermetabolic lung lesions. (a) A CT revealed two nodules in the bilateral upper lung lobes. (b) PET imaging indicated abnormal fluorodeoxyglucose (FDG) uptake in the nodules. (c) A 3-dimensional maximum intensity projection reconstruction of the PET images demonstrated abnormal FDG uptake in the lung and lymph nodes.

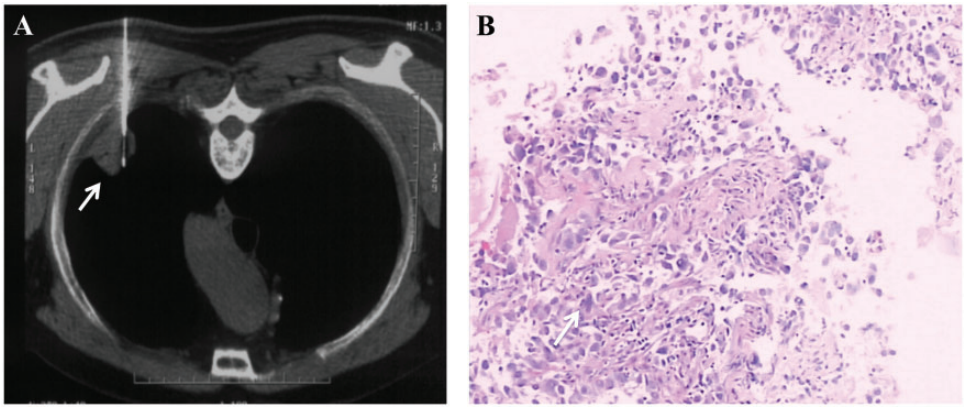

Figure 2. Computed tomography (CT)-guided percutaneous transthoracic lung biopsy showing adenocarcinoma. (a) A CT-guided percutaneous transthoracic needle biopsy was performed on the mass in the left upper lobe. (b) Histopathology (hematoxylin and eosin staining) revealed adenocarcinoma.

performed (Figure 3A c). Follow-up over a 6-month period with thoracic CT indicated that the tumor was clinically stable (Figure 3B c and d).

In September 2015, the patient presented with a stuffy nose, orbital and cheek pain, intermittent fever, and an axillary temperature of 37.2 to 39°C. Sinus CT demonstrated left sinusitis (Figure 4A and B). The patient was admitted to the otolaryngology department for sinus surgery. Histopathology confirmed sinusitis (Figure 4C) but the patient's fever persisted.

In November 2015, thoracic CT revealed new nodules in the right lung lobe (Figure 5A). Blood tests showed a serum creatinine level of 132.1 μmol/L, proteinuria (1765 mg/24 hours; reference

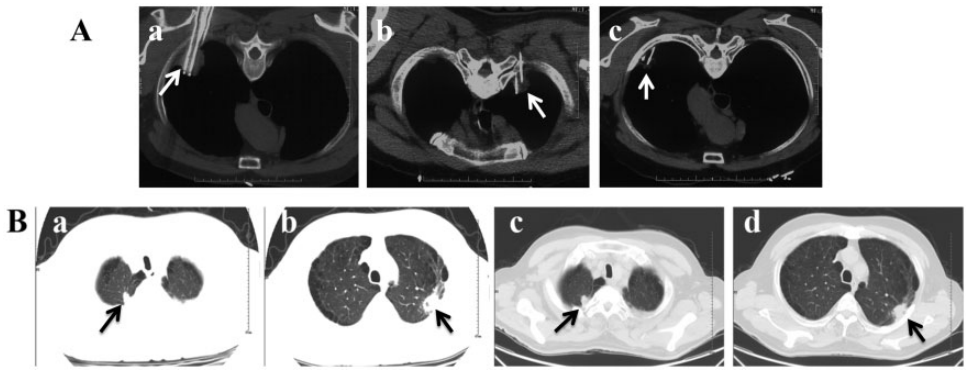

Figure 3. Lung masses and lesions after computed tomography (CT)-guided cryoablation and chemotherapy. (a) CT after cryoablation of the mass in the left upper lung lobe (a, April 2013), the nodule in the right upper lung lobe (b, April 2013), and the nodule in the left upper lung lobe (c, May 2014). (b) The lung lesions were evaluated after cryoablation and chemotherapy, showing that the right upper lobe lesion had decreased in size, whereas the left upper lobe nodule had not (a and b, May 2014). Follow-up in October 2015 showed that both lesions, in the left and right upper lobes, had decreased in size (c and d).

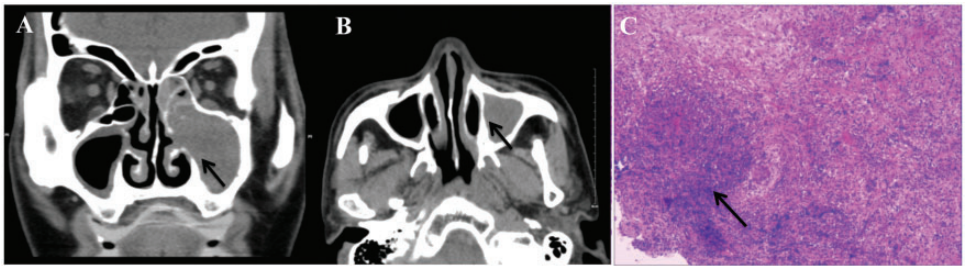

Figure 4. Sinus computed tomography (CT) and hematoxylin and eosin-stained sections. Sinus coronal (a) and axial (b) CT images revealed soft tissue filling in the left maxillary sinus, with additional soft tissue in the bilateral ethmoid sinus and right maxillary sinus. (c) Histopathology after sinus surgery (hematoxylin and eosin staining) indicated sinusitis.

range: 0–150 mg/24 hours) with hematuria, an elevated PR3-ANCA titer (423.6 relative units [RU]/mL; reference range: 0–20 RU/mL), and negative results on anti-glomerular basement membrane testing. Histopathology of an ultrasound-guided percutaneous renal biopsy demonstrated pauci-immune necrotizing crescentic glomerulonephritis (Figure 6). The diagnosis was AAV and GPA with renal, nose, and lung involvement. The patient received corticosteroids (intravenous methylprednisolone, 250 mg, once daily for 3 days, then oral methylprednisolone, 0.5 mg/kg, once daily and reduced by 8 mg every 4 weeks), plasmapheresis (six times in November and December 2015), intravenous cyclophosphamide (600 mg on Day 1 and 400 mg on Day 4, every 5 weeks, eight times, for a cumulative dose of 8000 mg), and methylprednisolone maintenance therapy (oral methylprednisolone, 10 mg, once daily). Following treatment, the patient's fever subsided. In July 2016, thoracic CT revealed that the pulmonary lesions and new nodules had decreased in size or disappeared (Figure 5B). By January 2017, the patient's PR3-ANCA titer had decreased

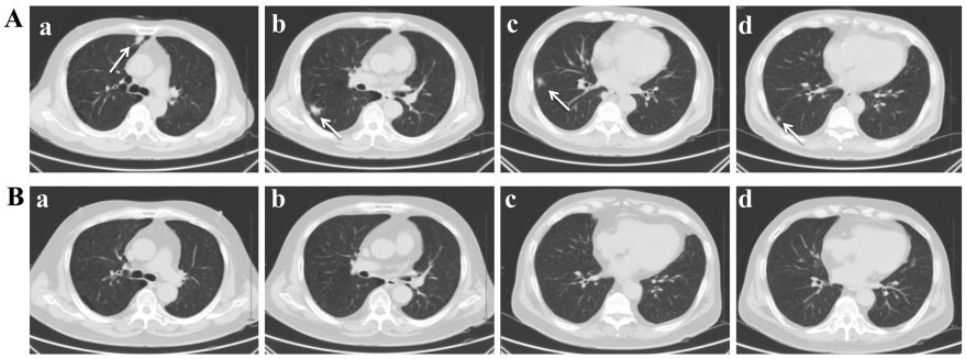

Figure 5. New nodules in the right lung in November 2015. (A) Chest computed tomography (CT) revealed new nodules in the right lung (a–d). (B) The nodules disappeared (a–d) after treatment using corticosteroids, plasmapheresis, and intravenous cyclophosphamide, followed by maintenance therapy with methylprednisolone.

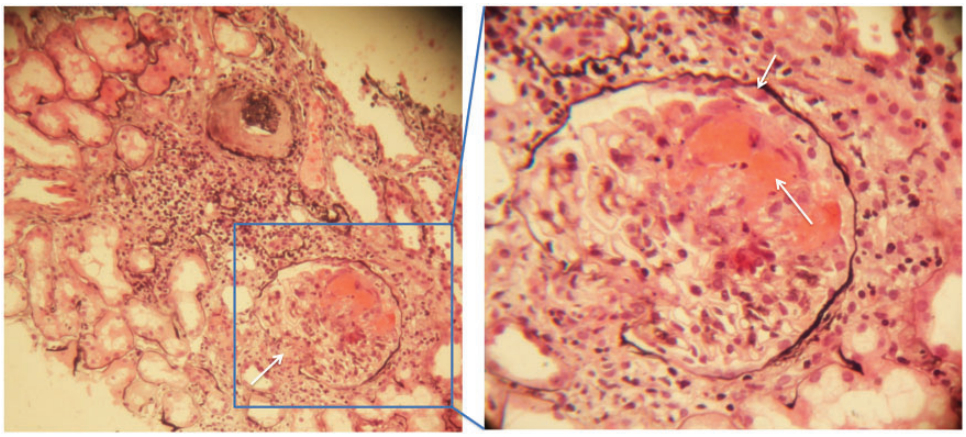

Figure 6. Histological examination (hematoxylin and eosin staining) of the ultrasound-guided percutaneous renal biopsy specimen revealed pauci-immune necrotizing crescentic glomerulonephritis.

to 106.5 RU/mL. The patient did not relapse while receiving cyclophosphamide, and oral methylprednisolone sustained remission.

In May 2017, the patient was readmitted for cough with sputum and fever. Laboratory testing showed a white blood cell count of 13.2×10^9/L (reference range: $3.97–9.15 \times 10^9$/L), a C-reactive protein level of 132.7 mg/L, a serum creatinine level of 280.3 μmol/L, and an elevated PR3-ANCA titer (366.4 RU/mL). Urinalysis demonstrated proteinuria (676.4 mg/24 hours) with microscopic hematuria. Thoracic CT revealed new lesions and pulmonary cavities in the bilateral lobes (Figure 7). The diagnosis was relapsing GPA with renal and pulmonary involvement and pulmonary infection. Progression of lung cancer could not be completely excluded, but the patient declined a biopsy. The patient was treated with antibiotics, antifungal agents, intravenous methylprednisolone, hemodialysis,

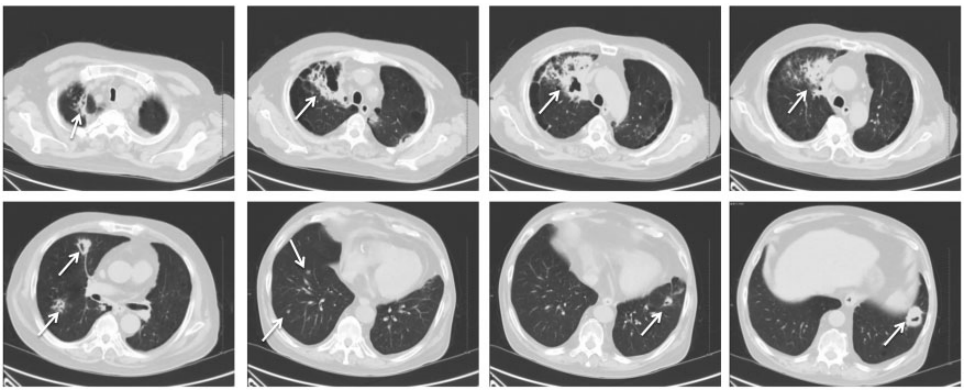

Figure 7. Chest computed tomography (CT) revealed new bilateral lung lesions in May 2017.

and plasmapheresis, but his condition did not improve. A few days later, the patient experienced atrial tachycardia and lost consciousness; cardiopulmonary resuscitation was performed. The patient did not respond to treatment and subsequently died. The patient's family refused autopsy; therefore, the possibility of lung cancer recurrence could not be excluded.

Discussion

There is increasing awareness of the association between malignant and autoimmune diseases in clinical practice.[6] Cancer may increase the risk of some autoimmune diseases, and patients with autoimmune diseases may be at a higher risk for cancer.[7,8] The mechanism underlying the bidirectional relationship between cancer and autoimmune diseases has yet to be elucidated.

AAV is an autoimmune disease that typically involves the upper and lower respiratory tract and kidney. Malignancy-associated vasculitis accounts for 0.4% to 4.2% of vasculitis cases.[9–11] Previous studies have shown that solid tumors and lymphoid and myeloid cancers can develop in patients with circulating ANCA.[2,9,12–14] Immunosuppressive treatment for AAV may accelerate the progression of malignant disease through immune suppression or by facilitating tumor immune evasion. Although rare, some reports have described the development of pulmonary malignant diseases in patients treated for AAV.[15,16] In the present case, AAV manifested after pre-existing cancer. The initial presentation included pulmonary nodules, which were diagnosed as lung adenocarcinoma on the basis of histopathology. Malignant disease was controlled by cryoablation and chemotherapy; subsequently, the patient showed clinical signs and symptoms of AAV. Other reports have described lung cancer preceding or coinciding with autoimmune diseases such as IgA vasculitis, pauci-immune necrotizing crescentic glomerulonephritis, and sarcoidosis.[17–20] The mechanisms by which cancer results in vasculitis are complex. Some speculate that tumors provoke inflammation, which may increase the risk of vasculitis in patients with cancer.[9,10,12,13] In the present case, the chemotherapy administered to treat the cancer likely predisposed the patient to AAV. Several other reports describe chemotherapy-associated vasculitis in patients treated for a pre-existing cancer.[21,22]

Differentiating pulmonary manifestations of GPA from malignant lung lesions using thoracic CT is challenging.

FDG-PET/CT imaging is an accurate tool for characterizing pulmonary nodules;[23] however, inflammatory lung lesions can mimic malignant tumors by presenting with similar hypermetabolic activity on FDG-PET/CT,[24] and this approach alone cannot be used to differentiate between inflammatory and malignant lesions in patients with GPA.[25] We recommend that PET/CT be used in combination with a clinical examination and laboratory testing to reach the correct diagnosis. In the present case, PET/CT revealed increased FDG uptake in the bilateral upper lung lesions and enlarged mediastinal and right hilar lymph nodes, which supported the suspected diagnosis of malignancy. Despite this, a diagnosis of lung cancer did not completely explain the findings on pulmonary imaging and biopsy or the entirety of the patient's clinical course. Therefore, we assumed that vasculitis was present before the pulmonary nodules developed, although there was no kidney involvement at that time. The patient initially underwent CT-guided percutaneous transthoracic lung biopsy for the mass in the left upper lobe. The diagnosis of lung cancer was confirmed, but the procedure provided a relatively small sample, and it is possible that the vasculitis could not have been seen in that specimen. Previous studies have suggested that transthoracic fine-needle aspiration may not be sufficiently accurate for diagnosing GPA with lung involvement.[26,27] In one report, a lung nodule removed using video-assisted thoracoscopic surgery was pathologically diagnosed as concurrent GPA and lung squamous carcinoma.[28] The characteristics of the right and left lung masses may have been inconsistent, and we did not repeat the biopsy for the mass in the right upper lobe to gain additional information regarding a diagnosis of vasculitis. Importantly, PET/CT did reveal soft tissue in the patient's left sinuses, which did not exhibit increased FDG uptake (Figure 8). We interpreted these findings as suspected vasculitis in the nose. Finally, the bilateral lung lesions did not

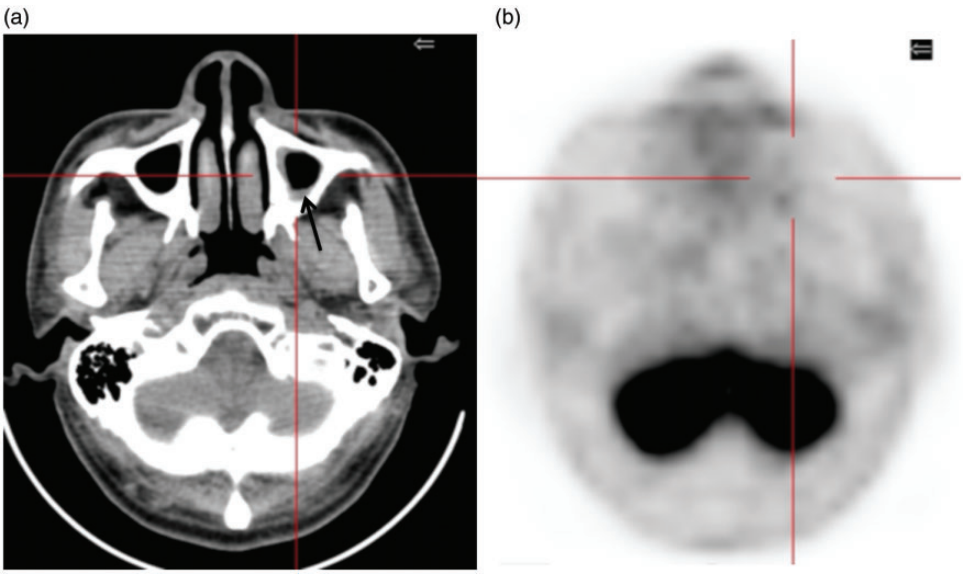

Figure 8. Computed tomography (CT) revealed left sinusitis. (a) CT revealed mild mucosal thickening in the ethmoid, sphenoid, and left maxillary sinus. (b) Positron emission tomography showed no remarkable fluorodeoxyglucose uptake in the sinuses.

significantly decrease in size after chemotherapy and cryoablation, but the left lung mass decreased in size and the right lung mass and new nodules disappeared after treatment using corticosteroids and intravenous cyclophosphamide. Thus, it is possible that the bilateral lung lesions were related to vasculitis. Unfortunately, the patient died after experiencing relapsing GPA with renal complications and pulmonary infection.

To our knowledge, this is the first published report of lung adenocarcinoma and granulomatous polyangiitis. These findings add to the clinical knowledge regarding the concurrent occurrence of malignant diseases and autoimmune diseases. Further research is required to understand the pathophysiological link between cancer and autoimmune diseases.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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