Lung cancer development in the patient with granulomatosis with polyangiitis during long term treatment with cyclophosphamide: first documented case

Midori Toriyama1, Etsuko Tagaya1, Tomoko Yamamoto2, Mitsuko Kondo1, Yoji Nagashima2 & Jun Tamaoki1

1First Department of Medicine, Tokyo Women’s Medical University School of Medicine, Tokyo, Japan.
2Department of Surgical Pathology, Tokyo Women’s Medical University Hospital, Tokyo, Japan.

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Abstract
A 65-year-old man was diagnosed with granulomatosis with polyangiitis (GPA) at the age of 47, when cytoplasmic anti-neutrophil cytoplasmic antibody (C-ANCA) serology was positive, and he had multiple nodular shadows in both lungs. He had been treated with prednisolone, cyclophosphamide (CPA) and plasma exchange. At the age of 64, a nodular shadow was newly detected in the right lower lung field and serum tumour marker increased. Subsequent positron emission tomography/computed tomography scan demonstrated accumulations of fluorodexyglucose (FDG) in the same area, mediastinum lymph nodes, thoracic wall, right iliac bone, and right retroperitoneum. The diagnosis of squamous cell lung cancer cT2bN2M1b Stage 4 was made with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). There are no reports of cases that lung cancer has developed with GPA during the long-term treatment with CPA. We suggest that in such patients, the differential diagnosis should include not only the relapse of GPA, but also the rare possibility of development of carcinomas.

Introduction
Granulomatosis with polyangiitis (GPA) is one of the ANCA-associated diseases (AAD). It is a necrotizing granulomatous vasculitis that typically involves upper and lower airways and kidneys. The common radiographic and computed tomographic (CT) abnormalities include multiple lung nodules and masses, where cavitations are often present in most nodules more than 2 cm in diameter. Given various clinical presentations, the diagnosis of GPA can be challenging and difficult to distinguish from other diseases such as tuberculosis, lung cancer, and sarcoidosis. We report a rare case of GPA with lung cancer developed while taking long-term cyclophosphamide (CPA).

Case Report
A 65-year-old Japanese man was diagnosed with GPA at the age of 47, when C-ANCA (PR3-ANCA) serology was positive, and he had multiple nodular shadows in both lungs (Fig. 1). He underwent diagnostic biopsies in nasal mucosa, lung, and kidney, and the histopathology revealed extensive necrotizing supplicative granulomatous inflammation, which was consistent with GPA. He had been treated with prednisolone (PSL), CPA, and plasma exchange since the diagnosis was made. At the age of 64, a nodular shadow was newly detected in the right lower lung field (Fig. 2). We suspected the relapse of GPA and increased the dose of PSL, but the size of the tumour shadow did not change. At the same time, the serum tumour marker gradually increased (squamous cell carcinoma antigen (SCC): from 3.2 to 6.2 ng/mL). We suspected malignant tumour and performed a positron emission tomography/computed tomography (PET/CT) scan, which showed accumulations of fluorodexyglucose (FDG) in the same area, mediastinum lymph nodes, thoracic wall, right iliac bone, and right retroperitoneum (Fig. 2). He was admitted to our hospital to undergo diagnostic bronchoscopy with
endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). He had a smoking history of 56-pack-year. Physical examination revealed decreased respiratory sounds in the right middle and lower lung fields. Laboratory findings on admission showed renal dysfunction and high levels of serum C reactive protein, C-ANCA and tumour markers (SCC 11.7 ng/mL, cytokeratin 19 fragments (CYFRA) 20.1 ng/mL). Chest X-ray on admission revealed an irregular opacity and collapse in the right lower field. PET/CT demonstrated increased uptake in the right lower lung nodule, mediastinum lymph nodes, thoracic wall, right iliac bone, and right retroperitoneum. We then performed EBUS-TBNA, and TBNA revealed neoplastic cell sheets in necrotic debris, which were diagnosed as squamous cell carcinoma (Fig. 2). Chemotherapy was performed, but the treatment was not effective, and he died 1 year after the diagnosis of lung cancer.

Discussion
Granulomatosis with polyangiitis, which was formerly named Wegener’s granulomatosis classically involves the triad of the upper respiratory tract, lungs, and kidneys. It is known that C-ANCA shows high sensitivity and specificity for GPA, with a sensitivity of 63.5–91% and specificity of 99–99.5% [1]. C-ANCA may also correlate with the disease activity, but there is a report that only 40% of patients exhibit an increased ANCA level upon relapse of GPA. In our patient, C-ANCA was positive but did not elevate at the age of 64 when a nodular shadow was newly detected. Thus, we could not conclude the relapse of GPA.

The most common radiographic and CT abnormalities of GPA are lung nodules and masses, which are usually multiple. Cavitations, air-space, and ground-glass opacities are also common. Cordier et al. reported that, in 77 patients with pulmonary GPA, 69% had nodules, 25% solitary nodules, and 49% cavitations [2]. Our patient at the time of diagnosis of GPA had multiple nodules and masses with central necrosis in the right lower lobe, which was characteristic for GPA. A differential diagnosis suggested infections of tuberculosis or aspergillosis, or malignancy such as malignant lymphoma for the patients with pulmonary nodules with cavity by taking immunosuppressants for a long
time. As the result of the EBUS-TBNA, both mycobacterial and fungal culture were negative. Furthermore, there were no histopathological findings of malignant lymphoma.

Current standard therapy for GPA combines corticosteroids and CPA to induce complete remission and maintenance. CPA is metabolized in the liver to chloromethine metabolites and acrolein. The chloromethine metabolites are responsible for CPA’s therapeutic effects. On the other hand, acrolein is teratogenic and toxic to bladder mucosa, thereby playing a role in the development of bladder cancer and haemorrhagic cystitis [3]. Indeed, it is reported that risk of bladder cancer increased when cumulative CPA dose exceeded 50 g [4]. The estimated incidences of bladder cancer after first exposure to CPA are 5% at 10 years, and 16% at 15 years [4]. In the present patient, cumulative dose of CPA was about 200 g and the duration was 12 years, which could be the risk of carcinogenesis. Although CPA is an effective drug for inducing remission of GPA, we should consider less toxic immunosuppressants such as azathioprine, methotrexate, and rituximab for maintenance therapy.

There have been no reports of an association between AAD and malignancies. In contrast, another study, which included malignancies diagnosed before and within 6 months after the diagnosis of vasculitis, concluded that malignancies are more frequent in AAD than in the general population. Also, there are five case reports of AAD and lung cancers occurring concurrently or within 2 years [5]. However, there are no reports of cases of lung cancer developing after such a long-term treatment of GPA. To our knowledge, we report the first documented case of GPA with lung cancer developing while taking long-term CPA. We suggest that in patients with GPA under treatment with long-term CPA, the differential diagnosis should include the rare possibility of lung cancer.

Disclosure Statements

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

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