



Case report

Axillary lymphadenopathy with IgG4 positive plasma cell infiltration as differential diagnosis of metastatic lung adenocarcinoma

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ABSTRACT

Immunoglobulin type G4 -related disease (IgG4-RD) is known as a chronic systemic inflammatory disease, which is sometimes associated with lung cancer. However, the detailed association between IgG4-RD and lung cancer in clinical settings is still poorly understood. An 80-year-old man was diagnosed with progressive lung adenocarcinoma carrying an EGFR point mutation at L858R, and osimertinib treatment was administered. Two months later, although osimertinib treatment showed good response to the primary tumor, fever and anorexia appeared, and multiple lymph nodes, in particular in the left axillary, became swollen. Ultrasonography-guided biopsy of the axillary lymph node revealed infiltration of lymphocytes with IgG4-positive plasma cells and fibrosis. Serum IgG4 levels were also increased. These results suggested that the multiple swollen lymph nodes were not metastasis, but IgG4-related disease. Based on these results, therapy using prednisolone was initiated. Multiple lymphadenopathy gradually decreased, and his symptoms improved. Currently, his good responses to osimertinib treatment have been maintained. Like in our case, multiple lymphadenopathy with IgG4-positive plasma cell infiltration during successful anti-cancer treatment is quite rare. In this case, it was hypothesized that anti-cancer treatment with osimertinib induced IgG4-positive plasma cell infiltration in multiple lymph nodes. When lymphadenopathy occurs during lung cancer treatment, IgG4-RD has to be considered other than lung cancer metastasis.

1. Introduction

Immunoglobulin type G4-related disease is a chronic systemic inflammatory disease [1], which rarely has a respiratory region. It is called IgG4-related lung disease (IgG4-RLD) [2]. Recently, a small number of reports have shown that it is related to primary lung cancer [3–7]. The incidence of cancer in IgG4-related disease was 3.5 times higher than that in the general population [8]; however, the association of lung cancer with IgG4-RD has remained unclear. Herein, we report a rare case of primary lung cancer, in which the patient developed IgG4-RD in the axial lymph node during EGFR-TKI treatment.

2. Case report

An 80-year-old man was diagnosed with lung adenocarcinoma carrying the EGFR point mutation at L858R; he was admitted to our hospital for treatment. He had no history of smoking or drinking and no

allergic constitution. Lung computed tomography (CT) scan showed left upper lung tumor and hilar and mediastinal lymph node enlargement (Fig. 1). There were no metastatic regions; therefore, the clinical stage was characterized as cT3N3M0 stage IIIc. Normally, chemoradiation is performed. However, considering his age and complications such as hypertension, paroxysmal atrial fibrillation, and pneumoconiosis, osimertinib therapy was initiated at a dose of 80 mg per day. Two months later, he showed symptoms of fever and anorexia. His left axillary was swollen with pain. The levels of C reactive protein (6.79 mg/dl), serum immunoglobulin G (IgG) (1888 mg/dl), G4 (IgG4) (137 U/ml), and E (IgE) (603 U/ml), and serum soluble IL-2 receptor (1150 U/ml) were elevated. Although the size of the primary tumor clearly reduced (Fig. 2A), multiple lymph nodes including the left axillary around the abdominal artery were enlarged, and the fat around the aorta to pelvic area was cloudy (Fig. 2B). To confirm metastatic lymphadenopathy, ultrasonography-guided biopsy of the axillary lymph node was performed. Histological analysis showed infiltration of lymphocytes and plasma cells with fibrosis (Fig. 3C and D). Immunohistochemistry

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Abbreviations

AIP	Autoimmune pancreatitis
CT	Computed tomography
HPF	High-power visual field

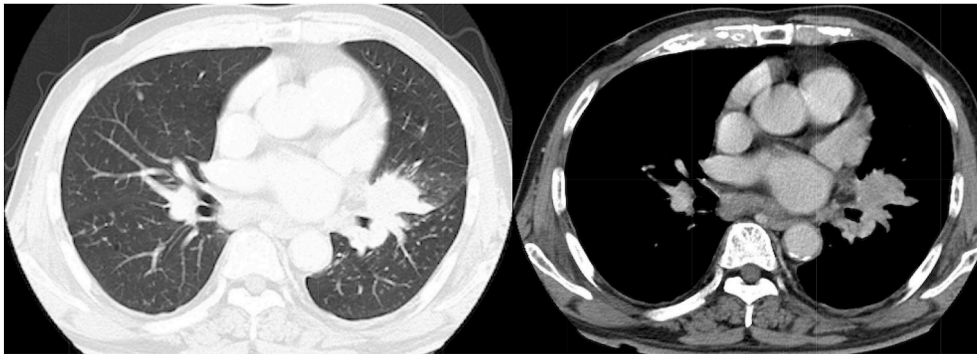


Fig. 1. CT scan before the initiation of osimertinib showed a primary tumor in left upper and lower lung and lymphadenopathy of hilar and mediastinum.

indicated IgG4-positive plasma cell infiltration with an over 30 cell count per high-power visual field (HPF) and an IgG4 to IgG ratio of more than 40% (Fig. 3E and F). According to these findings, multiple swollen lymph nodes were diagnosed with IgG4-related disease. Prednisolone (0.6 mg/kg/day) was administered, and improvement of his symptoms and multiple lymphadenopathies was observed (Fig. 4).

3. Discussion and conclusion

IgG4-RD is rarely observed in primary lung cancer patients, and it is sometimes difficult to distinguish it from lung cancer metastasis. In previous reports, malignancies in IgG4-RD were more likely to be diagnosed than those in the normal population [8], and a close association has been observed between IgG4-RD and malignancy formation within 12 years after diagnosis, particularly during the first year [9]. There have been several reports regarding IgG4-RD in lung cancer patients [3,5,6]; however, the association of lung cancer with IgG4-RD remains unclear. No study has reported that a new axillary lymph nodule of IgG4-RD developed during EGFR-TKI treatment for lung adenocarcinoma. In our case, primary lung cancer decreased effectively after EGFR-TKI; thus, differential diagnosis of the enlarged axillary lymph node was very important.

The pathological mechanisms between IgG4-RD and lung cancer was not completely elucidated; however, multiple immune-mediated mechanisms based on the fibroinflammatory process of IgG4-RD, such as genetic risk factor, bacterial infection, molecular mimicry, and autoimmunity, have been proposed. As for the pathological pathway, Th2 cell reaction, regulatory immune reaction, and transforming growth factor β (TGF- β) are thought to play a central role in it [10]. Recently, lung cancer treatment for immune checkpoint blockade was reported, in which antitumor immunity was increased by blocking intrinsic down-regulators, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand programmed cell death ligand 1 (PD-L1) [11]. If intrinsic immune systems for the tumor are intact, cancer antigens also could induce Th2 immune reaction including IgG4. In our case, osimertinib showed an effective tumor reduction (Fig. 2A). In contrast, multiple lymph nodes became swollen and dirty fat signs appeared in the retroperitoneum (Fig. 2B). This clinical course suggested that the cancer antigens released by osimertinib could be a trigger for not only Th2 immune reaction but also for regulatory T cell

(Treg) and TGF β signaling cascades.

Several case reports have focused on the co-existence of IgG4-RD and lung cancer. In two cases, IgG4-RD was diagnosed prior to lung cancer [3,4], and in two other cases, the co-existence of IgG4-RD with lung cancer was reported [5,6]. In these reports, lung cancer tissues were involved in the IgG4 positive cell proliferation. These cases suggested that IgG4 positive cell infiltration induced by Treg could cancel the repression of cancer growth, and then, IgG4-RD might promote the

carcinogenesis of lung cancer. However, another case in which the opposite clinical course was observed has also been reported. In this case, IgG4-positive infiltration was diagnosed during a routine follow up examination 4 years after lung resection for squamous cell carcinoma [7]. Lung cancer was also diagnosed prior to IgG4 positive infiltration, similar to this case. These cases suggested that there might be another pathological mechanism between IgG4-RD and lung cancer.

Recently, Shiokawa et al. reported IgG4-positive plasma cell infiltration in the cancer regions and relapse of autoimmune pancreatitis (AIP) [12]. Patients concurrently diagnosed with AIP and cancer showed IgG4-positive plasma cell infiltration in the tissues surrounding the tumor cells. All AIP patients with abundant IgG4-positive plasma cell infiltration had not developed a relapse of AIP after successful cancer treatment. This report suggested that AIP with IgG4 positive plasma cell infiltration might be a paraneoplastic syndrome of lung cancer. In our case, IgG4-RD occurred two months after lung cancer treatment initiation. Tumor size was immediately decreased after osimertinib administration. This might have produced the tumor antigens, leading to IgG4 positive plasma cell infiltration in the systemic regions.

In conclusion, we report a rare clinical course in which IgG4-positive plasma cell infiltration on the systemic lymph nodes was observed after lung cancer treatment. IgG4-RD sometimes leads to an inflammatory pseudotumor which is histologically IgG4-positive plasma cell rich [13]. However, the correlation between IgG4-RD and lung cancer well is not understood. Therefore, the possibility of IgG4 positive plasma cell infiltration in lymph nodes and the formation of a pseudotumor with IgG4-positive cell infiltration must be considered during lung cancer treatment in clinical settings.

Authors' contributions

YI managed the patient, created the figures, and collected laboratory data. YI and MH wrote the manuscript. YI, MH, NK, TK, KI, EM, MU, SM, MT, and NK contributed to the discussion of results and reviewed the manuscript. All authors read and approved the final manuscript.

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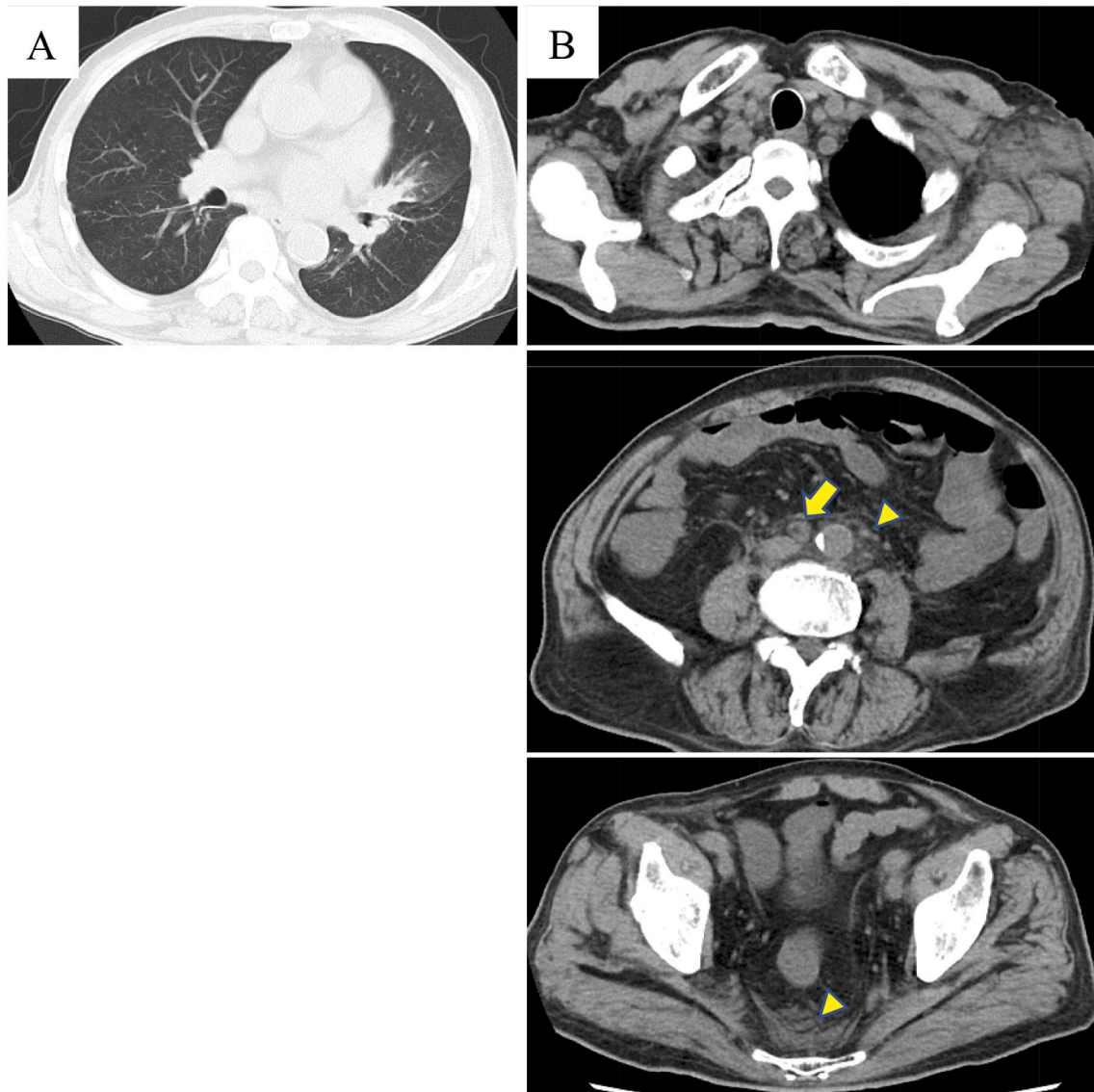


Fig. 2. CT scan after two months of osimertinib treatment. (A) The primary tumor can be seen to be shrinking. (B) The upper panel shows left axillary lymph node enlargement. The middle and bottom panels show paraaortic lymphadenopathy (arrow) and dirty fat signs in the retroperitoneal region (arrowheads).

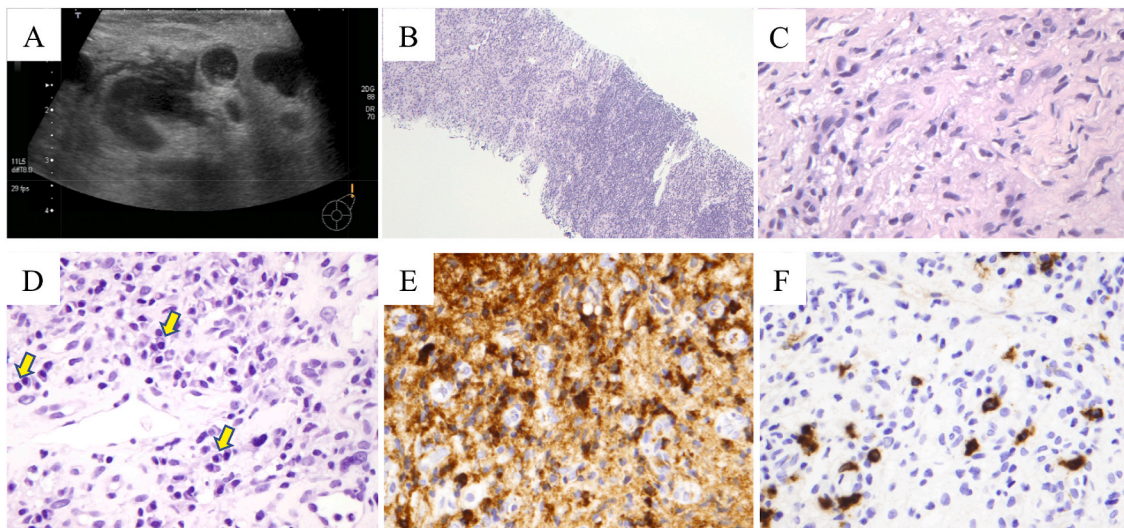


Fig. 3. (A) Ultrasound image of the left axilla lymph node. (B) ~ (E) Histopathological findings of the left axilla lymph node biopsy specimen. (B) Hematoxylin and eosin (HE) stain; $\times 40$. (C) HE stain; $\times 400$. Bundled fiber findings. (D) HE stain; $\times 400$. Dense infiltration of lymphocytes and plasma cells. The arrow indicates plasma cells. (E) Immunohistochemical staining for IgG, $\times 400$. (F) IgG4, $\times 400$. IgG4-positive plasma cells >30 /HPF, IgG4/IgG cell ratio was approximately 50%.

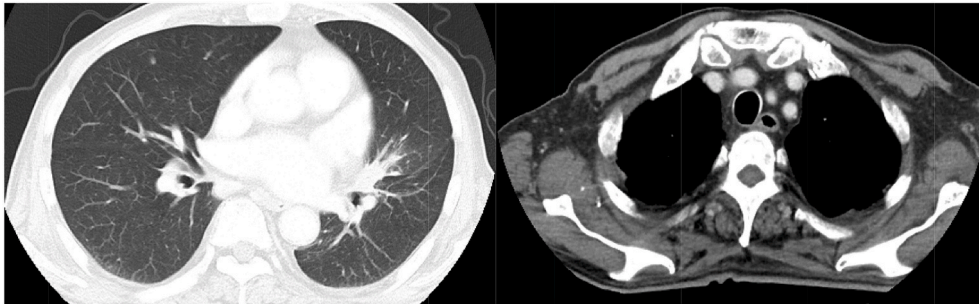


Fig. 4. CT scan after prednisolone administration. The tumor size slightly reduced, and the axillary lymph node was completely diminished.

Ethical approval

Not required as the event described was a part of routine service.

Consent

Written consent was obtained from the patient.

Guarantor

Naoki Koshimizu is a guarantor of this study.

Declaration of competing interest

The authors declare no conflicts of interest associated with this manuscript.

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