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CASE REPORT

Radiological findings and clinical features of thoracic immunoglobulin G4-positive plasma cell granuloma: two cases

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ABSTRACT. Plasma cell granulomas, inflammatory pseudotumours and myofibroblastomas are synonymous with characteristic plasma cell infiltration in various body organs including the pancreas, liver, retroperitoneum and mediastinal structures causing idiopathic fibrosclerosis. Recently, a new concept has arisen regarding the relationship between immunoglobulin (Ig)G4-positive cell infiltration and idiopathic systemic fibrosclerosis. We report two cases showing IgG4-positive cell infiltration in the lung presenting as lung nodules with or without extrapulmonary manifestations.

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Plasma cell granulomas are well-known disease entities that cause characteristic idiopathic fibrosclerosis of various body organs including the pancreas, liver, retroperitoneum and mediastinal structures. Such disease entities have been termed as inflammatory pseudotumours, myofibroblastoma, idiopathic multifocal fibrosclerosis or xanthofibrogranulomatosis [1]. In 2001, when immunoglobulin (Ig)G4-positive cell infiltration was reported in autoimmune pancreatitis, a new concept arose of an autoimmune systemic disorder within the category of IgG4-related disorders [2]. Further case reports have confirmed the relationship between IgG4-positive cell infiltration and idiopathic multifocal fibrosclerosis [3–5]. Taniguchi et al [5] reported IgG4-positive cell infiltration in the lungs of patients with autoimmune pancreatitis. In this report, we discuss two cases showing IgG4-positive cell infiltration in the lung presenting as lung nodules with or without extrapulmonary organ involvement.

Case report

Case 1

A 51-year-old man visited our hospital complaining of dyspnoea and abdominal pain of 15 days' duration. The patient had a medical history of recovery from bilateral pleurisy of unknown aetiology after thoracentesis and antibiotic treatment six years previously. On laboratory examination, his white blood cell count was 14 600 mm^{-3}, and his neutrophil percentage was 71.4%. His serum rheumatic factor, fluorescent antinuclear antibody (FANA), antineutrophil cytoplasmic antibody (ANCA), anti-double-stranded DNA and antiribonucleoprotein+ smooth muscle (antiRNP+Sm) levels were within normal limits. As he complained of cough and sputum production, a chest radiograph and a CT scan were performed to evaluate for possible pneumonia. The chest radiograph revealed a right hilar mass, and the CT scan showed a lobulated mass in the right middle lobe with multiple irregular nodules in the right upper and middle lobes (Figure 1a–c). The patient underwent percutaneous core needle biopsy of the right middle lobar mass, which showed organising pneumonia without malignant cells. As malignancy was clinically suspected, the patient underwent video-assisted thoracoscopic biopsy (VATS) of the right middle lobar mass; the VATS specimen revealed organising pneumonia consistent with plasma cell granuloma; however, IgG4 immunochemical staining was not performed at that time. During the outpatient follow-up, our patient underwent an abdominal CT scan for evaluation of acute abdominal pain. His abdomen CT scan demonstrated diffuse gallbladder wall thickening with perforation, probably indicating acute cholecystitis (Figure 1d). After percutaneous transhepatic choledochostomy, a choledochoscopic biopsy of the gallbladder was obtained and showed chronic active inflammation with erosion and granulated tissues; IgG4-specific immunohistochemical staining showed immunoreactive plasma cells (more than 50 cells in each high-power field). IgG4 immunohistochemical staining of the earlier VATS specimen was also performed and revealed IgG4-positive plasma cell infiltration (again more than 50 cells in each high-power field) (Figure 1e,f). High-dose steroid treatment was started after confirmative diagnosis of IgG4-related fibrosclerosis. A follow-up chest CT scan after high-dose steroid therapy for three months showed marked improvement of the previously noted mass in the right middle lobe and the other irregularly shaped nodules in the right lung.

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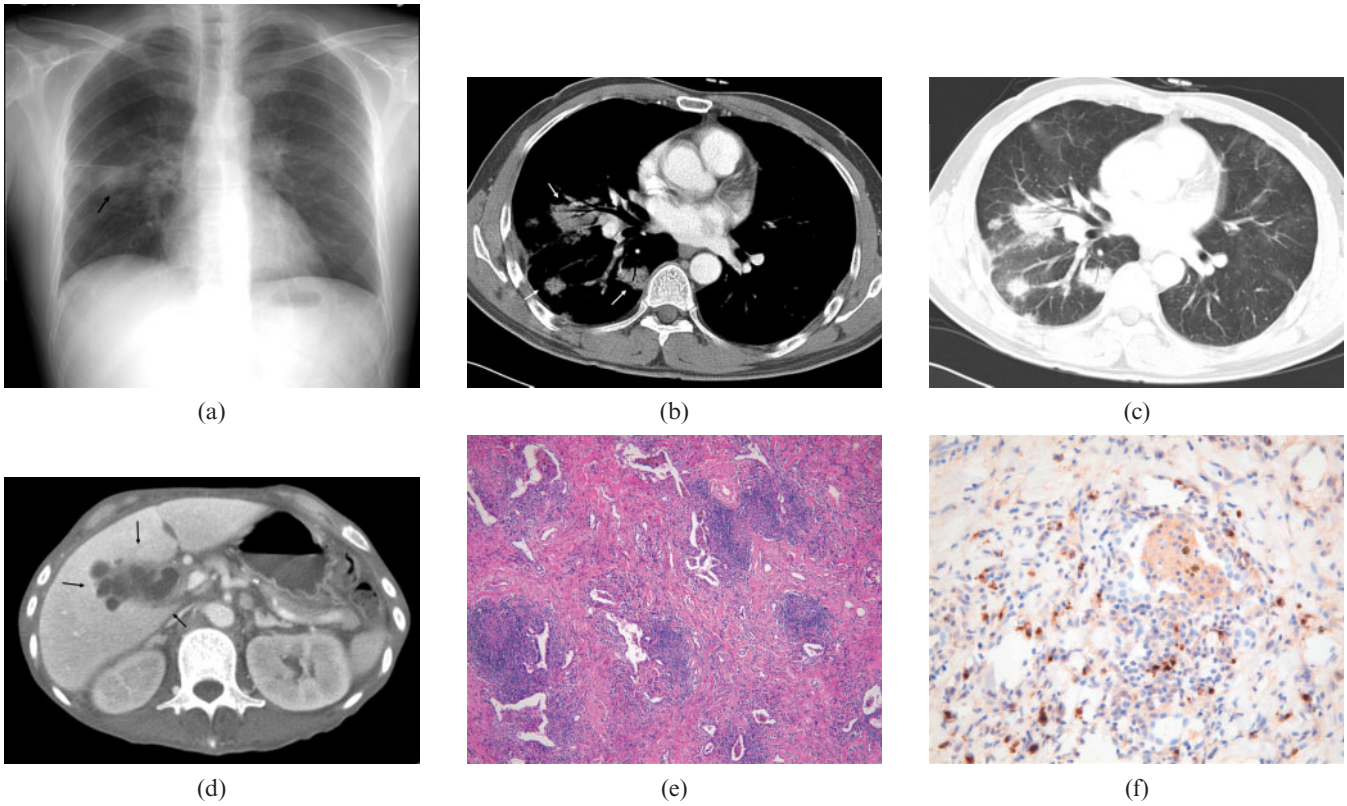

Figure 1. (a) Ill-defined patchy consolidation combined with peribronchial infiltrations are noted in the right middle lung field on the chest radiograph. (b, c) Axial contrast-enhanced CT scan shows an irregularly shaped mass-like consolidation containing air bronchogram in the medial segment of the right middle lobe that abuts both the major and minor fissures (arrows). Suspected direct invasion of the mass into the posterior segment of the right upper lobe and the anterior segment of the right lower lobe. Other multiple lobulating contoured nodules are seen in the right upper lobe and the right lower lobe. (d) Axial contrast-enhanced CT scan during the portal phase shows diffuse thickening of the gallbladder wall with a low attenuation lesion seen in the adjacent hepatic segment IV (arrows). This finding suggests intrahepatic abscess formation due to gallbladder perforation. (e) Photomicrograph of the histological specimen shows diffuse plasma cell infiltration in the interstitial tissue as seen on the low-power field (haematoxylin and eosin stain, ×100). (f) Photomicrograph of the immunoglobulin (Ig)G4 immunohistochemical staining shows diffuse immunoreactive plasma cell infiltration greater than 50 per high-power field (IgG4 stain, ×400).

Case 2

A 40-year-old woman was admitted to our hospital with mild dyspnoea of seven years' duration. Five years previously, she had been treated for pleural tuberculosis with antituberculosis medication at another hospital for 15 months. On admission to our hospital, the patient's laboratory examination showed a white blood cell count of $10\,800\,mm^{-3}$ and a neutrophil percentage of 71.3%. The C-reactive protein level was $9.30\,mg\,dl^{-1}$ (normal $>0.6\,mg\,dl^{-1}$). Her serum rheumatic factor, FANA, anti-double-stranded-DNA and antiRNP+Sm levels were all within normal ranges. Before she visited our institution, she had undergone several chest CT scans at another hospital for follow-up of her tuberculosis pleurisy. Her initial chest CT scan, obtained approximately 2 years ago, demonstrated multiple well-defined non-calcified nodules, and irregularly shaped mass-like consolidation with air bronchogram in the left upper and lower lobe. At that time, the lesions were suspected as the sequelae of previous pulmonary tuberculosis (Figures 2a,b). On her six-month follow-up CT scan, the mass-like consolidation had decreased in the left lower lobe; however, new irregularly shaped nodules appeared in the right upper lobe and left lower lobe (Figure 2c). As these findings were considered to indicate reactivation of her pulmonary tuberculosis, antituberculosis medication was restarted 1 year ago. The patient's last follow-up chest CT scan after admission to our institution revealed multiple new lung nodules along the subpleural region in the right lung and near-complete regression of the previous mass-like consolidation in the left upper lobe with mild fibrotic sequelae (Figure 2d). The radiological features were presumed to be due to systemic vasculitis, such as Wegener's granulomatosis or lymphoproliferative disorder; two core biopsies were performed on the right middle lobe and the right upper lobe lesions. The biopsy specimens yielded only non-specific inflammatory cells inadequate for diagnosis. A VATS biopsy of the right middle and upper lobe was then performed in order to confirm the diagnosis. The VATS specimen exhibited a lymphoplasmacytic, sclerosing inflammation with numerous IgG4-positive cells, *i.e.* more than 150 cells per high-power field, in the right middle lobe, and granuloma with caseous necrosis in the right upper lobe (Figure 2e,f). After diagnosis of IgG4-related fibrosclerosis, systemic work-up for other visceral organ involvement was performed by

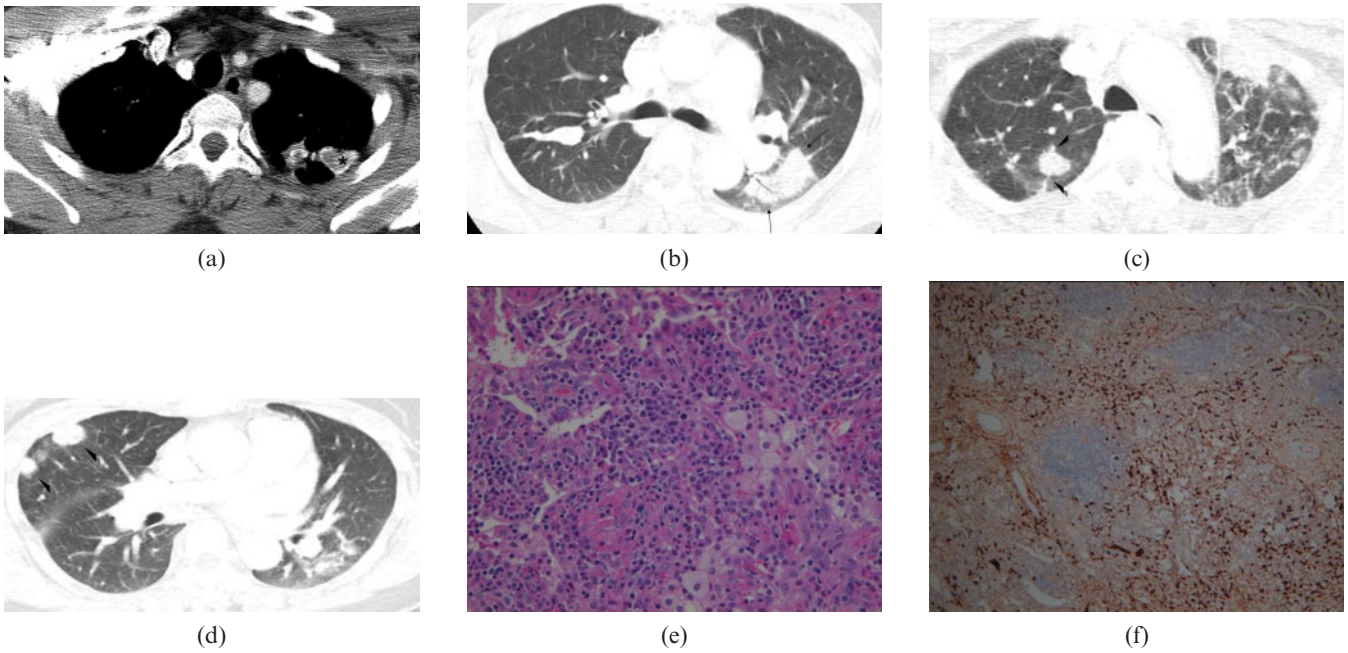

Figure 2. (a, b) Axial contrast-enhanced CT scan shows multiple well-defined, non-calcified nodules and irregularly shaped mass-like consolidation containing air bronchogram in the left upper lobe (lung window setting, arrows). In the apex of the left upper lobe, calcified granulomas are noted (asterisk). These lesions were considered to indicate pulmonary tuberculosis. (c) On the follow-up chest CT scan 6 months later, the size of the previous mass-like consolidation in the left upper lobe decreased, although a previously unseen, irregularly shaped nodule appears in the right upper lobe (arrowheads). (d) On the last follow-up chest CT scan obtained 1 month later, the previous mass-like consolidation in the left upper lobe shows complete regression with mild fibrotic sequelae. Multiple, new irregularly shaped nodules are noted along the subpleural region of the right upper and right lower lobe (arrowheads). (e) Percutaneous needle core biopsy specimen taken from the nodule in the right middle lobe. Plasma cells and mature lymphocytes infiltrate the alveolar septum (haematoxylin and eosin stain, ×400). (f) Photomicrograph of the immunoglobulin (Ig)G4 immunohistochemically stained biopsy specimen shows lymphoplasmacytic sclerosing inflammation with numerous IgG4-positive cell infiltrations, >150 per high-power field, suggesting IgG4-related fibro-inflammatory disease (IgG4 stain, ×100).

abdominal CT but showed no evidence of IgG4-related fibrosclerosis in the abdomen. High-dose steroid therapy using methyl-prednisolone was commenced and follow-up was planned.

Discussion

In our cases, lung involvement of IgG4-related fibrosclerosis was presented as multiple lobulated mass-like opacities with or without air bronchogram, irregularly shaped nodules, peribronchial infiltration and combined septal thickening in both lung fields. Prior reports have described lung involvement of IgG4-related fibrosclerosis as alveolar consolidation with the halo sign and a perihilar peribronchial distribution [6] or area of ground-glass attenuation in the middle and lower lobe, and honeycombing predominantly in the dorsal aspect of the lower lobes [5]. Compared with previous reports, our cases revealed more extensive mass-like consolidation and nodules, which may make the differential diagnosis difficult between IgG4-positive plasma cell granuloma and systemic vasculitis, pulmonary tuberculosis and lymphoproliferative disorders. Migrating patterns of lesions were helpful in exclusion of malignancy in our cases.

Previous reports identified a link between elevated serum IgG4 and idiopathic systemic fibrosclerosis with infiltration of IgG4-positive plasma cells in various organs [6–9]. The conditions of autoimmune pancreatitis, sclerosing cholangitis, Reidel's thyroiditis and mediastinal fibrosis are now suggested to belong to the same disease spectrum of IgG4-related fibrosclerosis [4, 7–9]. Several recent case reports described lung involvement of IgG4-positive plasma cell granulomas with or without extrapulmonary organ involvement [5, 6]. Zen et al [10] revealed that IgG4-positive plasma cell infiltration in the lung has histological similarity with autoimmune pancreatitis and they assumed that an IgG4-related immunological process might be involved in the pathogenesis of the lung lesions. We witnessed two cases showing IgG4-positive plasma cell infiltration in the lung: one case was combined with sclerosing cholangitis and the other did not have combined extrapulmonary organ involvement. Our patient had no symptoms suggesting systemic fibrosclerosis, such as sicca syndrome or pancreatitis. The pathology specimen demonstrated strong IgG4-positive cell infiltration (more than 150 cells per high-power field). Kobayashi et al [6] reported IgG4-positive pulmonary disease cases showing an HRCT pattern of alveolar consolidation, with a peribronchial distribution, peripheral ground-glass opacity and perihilar predominance, and which were initially diagnosed as lymphoma. In our patients, there were multiple lesions that either showed mass-like consolidation or showed ill-defined nodules with peribronchial

infiltration and combined septal thickening. Our patients were also initially suspected to have systemic vasculitis, lymphoproliferative disorders such as multicentric Castleman's disease, pulmonary tuberculosis or primary lung cancer with lymphangitic spread. However, in Case 1, follow-up CT scans revealed migration of the consolidation foci and lung nodules, which can be observed in follow-up studies, suggesting non-malignant lesions. The two cases showed no significant mediastinal lymphadenopathy on CT scan. Histology revealed that the nodules and consolidation foci consisted of IgG4-positive plasma cells and lymphocyte infiltration intermixed with irregular fibrosis. Surrounding linear opacities show that the inflammatory process extends to the interstitial septa [10]. The number of IgG4-positive plasma cells per high-power microscopic field of view has to be counted in order to establish the diagnosis of IgG4-positive fibrosclerosis. Infiltration in autoimmune pancreatitis will be considered moderate when 10–30 IgG4-positive plasma cells are identified in a high-power microscopic view. If more than 30 cells are visible, the infiltration is considered severe [11].

The disease may mimic lung neoplasm, manifested by consolidation foci surrounded by interstitial septal thickening, but lung involvement by IgG4-positive fibrosclerosis should be considered in the presence of high serum levels of IgG4. An understanding of disease entity of IgG4-positive fibrosclerosis and recognition of the radiological features of lung involvement are important in terms of tailoring treatment, because this entity may mimic other neoplastic conditions that should be surgically resected.

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