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Three cases of immunoglobulin G4-related respiratory disease with uncommon imaging findings

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Abstract. Background: Immunoglobulin G4-related disease (IgG4-RD) is a rare multisystemic idiopathic fibroinflammatory disorder. The rare form of IgG4-RD with isolated thorax involvement is called immunoglobulin G4-related respiratory disease (IgG4-RRD). IgG4-RRD, which is reported in a limited number of cases in the literature, can be categorized into four types on the prevalent chest computed tomography (CCT) findings: solid nodular, round-shaped ground-glass opacity, alveolar interstitial, and bronchovascular. Solid nodular form of IgG4-RRD with mass-like lesions is sporadic and described in the literature with a small number of case reports. **Objectives/Methods:** We aim to present the radiologic, pathologic, and clinical findings of three cases of IgG4-RRD mimicking lung cancer. **Results:** In all three patients, IgG4-RRD occurred with mass-like lesions in the thorax. In case-1 and 2, CCT showed multiple, nodular lesions and multiple mediastinal lymph nodes. On positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with computed tomography (18F-FDG PET/CT), the masses showed increased 18F-FDG uptake in case-2 and 3. The gold standard histopathological verification for IgG4-RRD was provided for all cases. **Conclusions:** IgG4-RD is an immune-mediated condition comprised of a collection of disorders that share particular pathologic, radiologic, serologic, and clinical features. Isolated IgG4-RRD is rarely seen and is available in the literature as case reports. IgG4-RRD, which can make lung involvement in different patterns, rarely appears with mass-like lesions. Still, IgG4-RRD must be considered in the differential diagnosis of mass lesions detected in CCT. Laboratory, radiological, and histopathological findings of the disease should be evaluated together for an accurate diagnosis.

Key Words: IgG4, Lung, Computed tomography.

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a multisystemic idiopathic fibroinflammatory disorder characterized by lymphoplasmacytic infiltration of tissues and organs abundant in immunoglobulin G4 (IgG4) plasma cells, obliterative phlebitis, and storiform fibrosis (1). Approximate incidence of IgG4-RD was detected in the 0.28 to 1.08 / 100,000 population, and no family IgG4-RD cases were recorded (2). Although the exact pathogenesis of IgG4-RD is not fully clarified yet a combination of autoimmunity and the allergic phenomenon is

thought to be responsible for the fibroinflammatory response in the disease (1).

Common histopathological findings, like tumefactive lesions, were found in the evaluation of the different organs affected. The three major pathologic features of IgG4-RD are lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis (3). IgG4-RD frequently affects the exocrine organs, including the pancreas, salivary glands, and lacrimal glands. However, it can also affect the liver, kidney, thyroid gland, biliary system, central nervous system, retroperitoneum, mesentery, and lymph nodes (3,4). Additionally, the disease may involve the lung parenchyma, airways, pleura, and mediastinum in the thorax (5). The rare form of IgG4-RD with isolated thorax involvement is called immunoglobulin G4-related respiratory disease (IgG4-RRD) (6). IgG4-RRD, which is reported in a limited number of cases in the literature, can be categorized into four types on the prevalent chest computed tomography (CCT) findings: solid nodular, round-shaped ground-glass opacity, alveolar interstitial, and bronchovascular (7). Solid nodular form of IgG4-RRD with mass-like lesions is rare but should be considered in the differential diagnosis of thoracic malignant lesions. Herein we present the radiologic, pathologic, and clinical findings of three cases of IgG4-RRD mimicking lung cancer.

Case Reports

Case 1

A 50-year-old female patient was admitted to the hospital with a cough and bloody sputum for two months. The patient who did not have any known disease in her medical history had a family history of coronary artery disease. On physical examination, vital values were within normal limits. In auscultation, there were rales in the bilateral lungs, more prominent in the lower lobes. Complete blood count values were normal. Chest X-ray demonstrated multiple rounded nodular and mass-like opacities in the middle and lower zones of both lungs (Figure 1). Non-contrast enhanced CCT was performed for further evaluation. Multiple, nodular, and mass-like lesions demonstrating air bronchogram sign in both lungs with peripheral and lower lobe-weighted distribution were observed (Figure 2). Besides, there were multiple mediastinal lymph nodes with a maximum short-axis diameter of 16 mm. With all these findings, vasculitis, sarcoidosis, primary or metastatic pulmonary malignancies were first considered in the differential diagnosis. In advanced laboratory tests, anti-neutrophil cytoplasmic antibody (ANCA) values were negative while, and the IgG4 value was eight times the normal, suggesting IgG4-RRD. Histopathological diagnosis of the transthoracic biopsy was reported as IgG4RRD. The control CCT obtained one week after corticosteroid treatment showed the lesions regressed almost completely, leaving fibrotic changes in place (Figure 3).

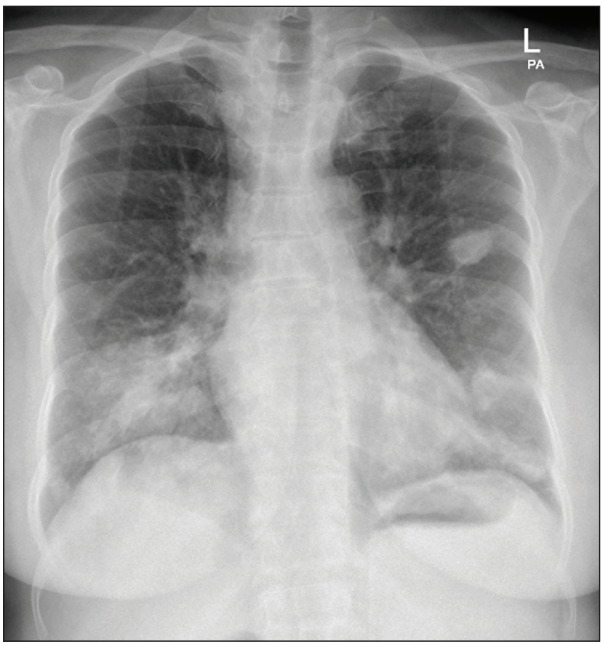

Figure 1: 50-year-old female patient's chest X-ray demonstrates multiple rounded, nodular and mass like pulmonary opacities in the middle and lower zones of both lungs.

Case 2

A 26-year-old female patient, who was diagnosed with colon cancer six years ago and whose treatment was completed, applied to the hospital for routine control. The patient had no clinical complaints and no findings on physical examination. Contrast-enhanced CCT scan demonstrated a 30x37x47 mm in size perihilar mass with a smooth contour and homogeneous internal structure (Figure 4a and b). Multiple mediastinal lymph nodes with a maximum short-axis diameter of 13 mm were seen (Figure 4c). On positron emission tomography with

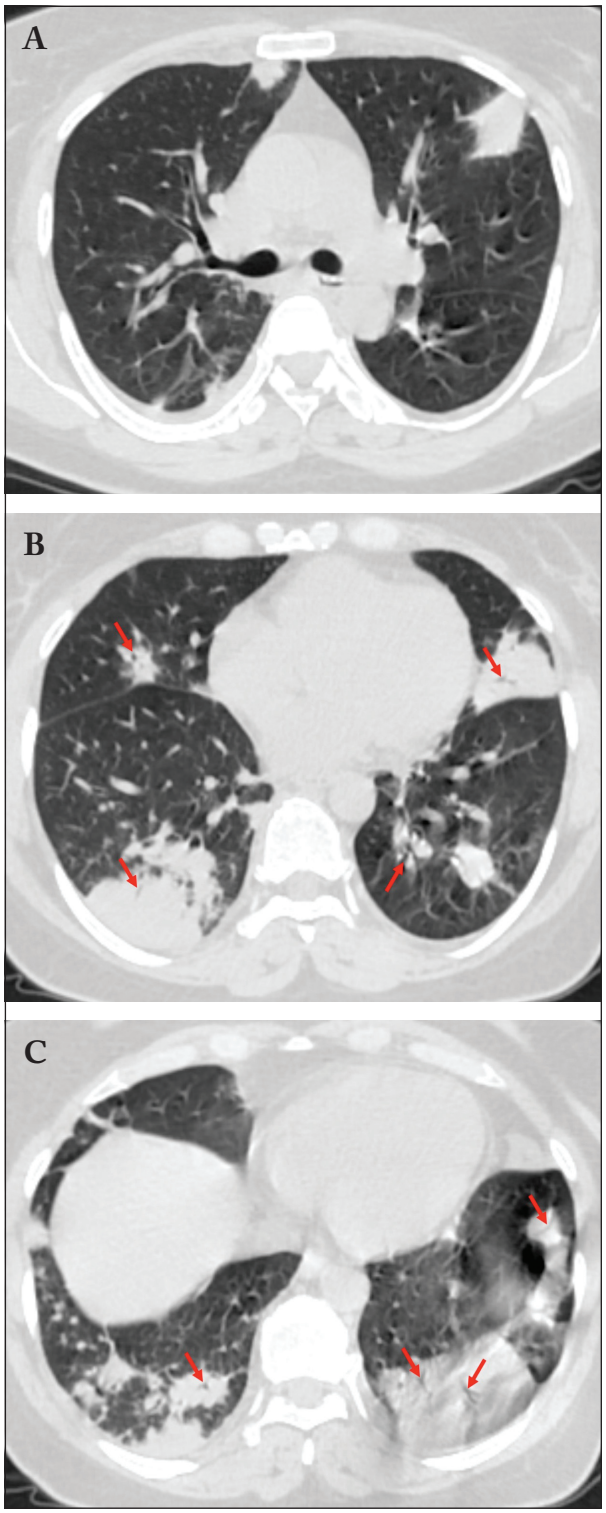

Figure 2: Axial images of non-contrast-enhanced chest computed tomography show multiple, nodular, and mass-like lesions in both lungs with peripheral and lower lobe-weighted distribution (a-c). Air bronchogram sign is observed in most of the lesions (arrows) (b, c).

2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with computed tomography (18F-FDG PET/CT), the mass showed a slightly increased 18F-FDG uptake (SUVmax: 2.7) (Figure 4d). In the magnetic resonance imaging (MRI) of thorax, the lesion was isointense with muscle in T1-weighted images, hyperintense in T2-weighted images, and enhanced homogeneously in post-contrast series. Upon the imaging findings and patient history, metastasis, primary lung cancer, lymphoma, and sarcoidosis were considered in the differential diagnosis. In laboratory tests, it was found that the IgG4 value was elevated with 723 mg/dL (135mg/dL). A surgical lung biopsy was performed, and the diagnosis was reported as IgG4-RRD.

Case 3

Non-contrast CCT of a 56-year-old asymptomatic male patient who had been routinely followed up due to the diagnosis of laryngeal cancer for one year demonstrated a newly emerging hypodense solid mass on the left side of anterior thoracic wall at the level of second costae. The mass measured 25x35x37 mm in size caused destruction in the adjacent costa and invaded the pectoralis muscle (Figure 5a and 5b). There was also an extension of the mass to the intrathoracic area with pleural thickening and reticulations in the adjacent lung parenchyma, suggesting invasion (Figure 5c). Several lymph nodes, the largest of which was 8x7mm in size, were observed in the left internal mammary chain (Figure 5d). In

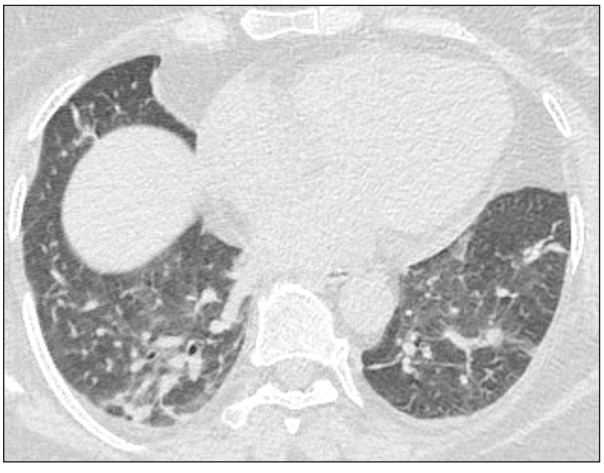

Figure 3: Axial image of non-contrast-enhanced chest computed tomography obtained X days after corticosteroid treatment shows that the nodules and masses disappeared leaving reticulations and ground-glass opacity behind.

18F-FDG PET/CT performed for further evaluation, increased F-18 FDG uptake (SUVmax: 12.0) was noted in the lesion (Figure 5e). In the differential diagnosis of the lesion, laryngeal cancer metastasis, haematological malignancies, tuberculosis, soft tissue sarcoma and malignant pleural mass were considered. After an excisional biopsy, the diagnosis of the lesion was reported as IgG4-RRD.

Discussion

IgG4-RD is an immune-mediated condition comprised of a collection of disorders that share particular pathologic, radiologic, serologic, and clinical features (8). Pancreas, liver, biliary tract, gastrointestinal tract, salivary and lacrimal glands, orbita, kidney, retroperitoneum, mesentery, thyroid, pituitary gland, prostate gland, meninges, skin, and lymph node involvement of this rare disease have been known (7,9,10). All lesions due to IgG4-RD within the borders of the thorax are classified as IgG4-RRD (6). Lung involvement due to IgG4-RD has been reported to be 13% in cases involving other organs and systems. As in our three cases, IgG4-RD diagnosed due to isolated lung involvement are extremely rare and described in the literature with a small number of case reports.

It has been reported that the frequency of the disease increases significantly in people with a history of asthma, atopic body, or cancer, as in our Case-2 with colon and Case-3 with laryngeal cancer.

IgG4-RRD may be asymptomatic, as in our cases or cough, hemoptysis, chest pain, and shortness of breath may occur in symptomatic patients (3,5).

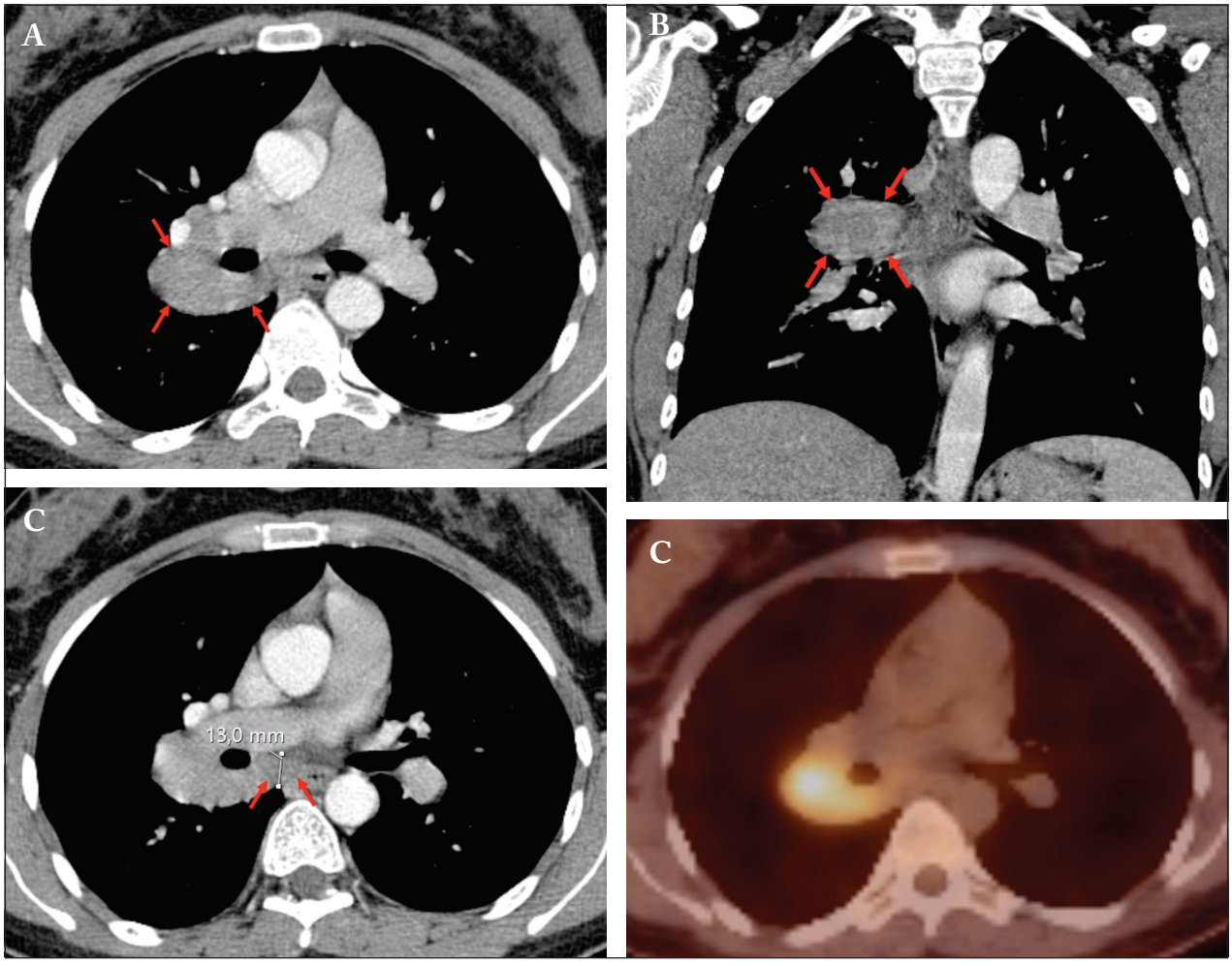

Figure 4: Axial (a) and coronal (b) images of contrast-enhanced chest computed tomography of a 26-year-old female patient shows a perihilar mass adjacent to the right main pulmonary artery, surrounding the right main and intermediate bronchus with a smooth contour and homogeneous internal structure. Multiple mediastinal lymph nodes with a maximum short-axis diameter of 13 mm are also detected (c). On positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography, the mass shows a slightly increased 18F-FDG uptake (SUVmax: 2.7) (d).

Constitutional symptoms are rarely reported (11). Pulmonary function testing shows a reduced diffusing capacity and restrictive dysfunction, particularly in the presence of extensive parenchymal infiltrations (12). While most IgG4-RRD patients like our three cases have elevated serum IgG4 concentrations, it is neither sensitive nor specific for diagnosis. Up to 30 per cent of patients with distinctive histopathological features may have normal serum IgG4 serum levels, and 5 per cent of the population may also have elevated IgG4 serum concentrations (13). Bronchoalveolar lavage (BAL) fluid analyses obtained via bronchoscopy have been reported to demonstrate increased levels of IgG4 and correlate with serum level IgG4 (14). BAL

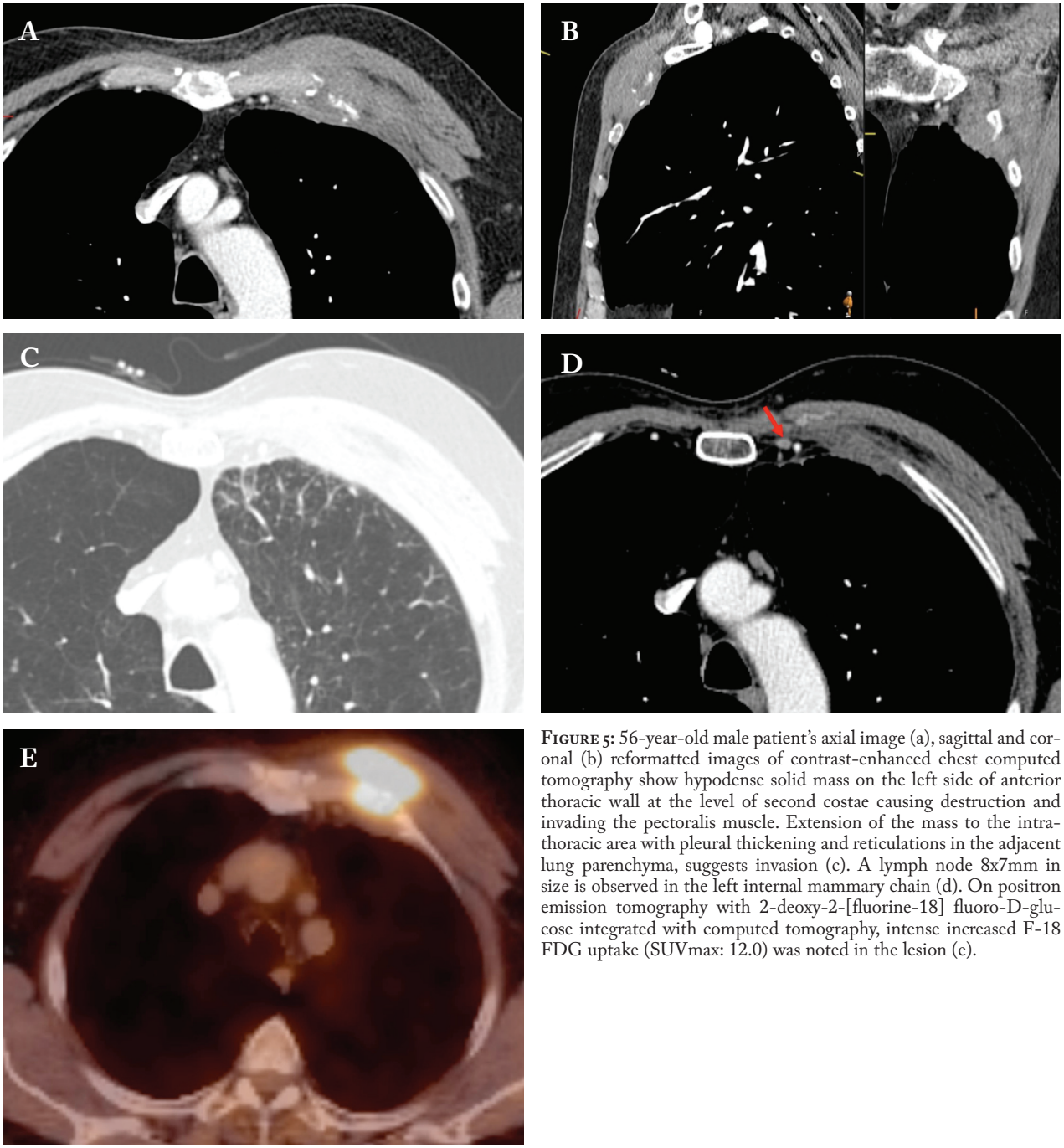

Figure 5: 56-year-old male patient's axial image (a), sagittal and coronal (b) reformatted images of contrast-enhanced chest computed tomography show hypodense solid mass on the left side of anterior thoracic wall at the level of second costae causing destruction and invading the pectoralis muscle. Extension of the mass to the intrathoracic area with pleural thickening and reticulations in the adjacent lung parenchyma, suggests invasion (c). A lymph node 8x7mm in size is observed in the left internal mammary chain (d). On positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography, intense increased F-18 FDG uptake (SUVmax: 12.0) was noted in the lesion (e).

cell analysis typically reveals lymphocytosis based on histopathological findings as expected.

As clinical signs and symptoms are nonspecific, IgG4-RRD is frequently unexpectedly identified by imaging observations and pathological evaluation. It is reported that in some asymptomatic individuals, IgG4-RRD can be detected incidentally by radiological imaging. Therefore, imaging methods such as CCT, MRI, and PET / CT play an essential role in the diagnosis of IgG4-RRD and even in the evaluation of response and surveillance to treatment (1,9). CCT is the most useful radiological imaging method in the diagnosis of IgG4-RRD (5,9). The most common CCT finding is the presence of enlarged lymph nodes in the hilar and mediastinal region, which can be seen in up to 90% of the patients (5,9). The other common findings observed in CCT are ground-glass opacity (GGO), nodule, thickening of bronchovascular bundles, interlobular septal thickening, bronchiectasis, honeycombing, cysts, pleural effusion, and pleural thickening in the paravertebral area (15,16). As in our patients, soft tissue masses (Case-3), and mass-like lesions (Case 1 and 2) are among the significant CT findings that can be seen in IgG4-RRD. Based on these CCT findings, IgG4-RRD is categorized into four different involvement patterns as solid nodular, bronchovascular, alveolar interstitial, and round-shaped ground-glass opacities (9). In the differential diagnosis of these findings detected in CCT, lung cancer, infections, vasculitis, idiopathic interstitial pneumonia, cryptogenic organizing pneumonia, multicentric Castleman disease, and sarcoidosis must be considered (17). Multiple nodules of IgG4-RRD may interfere with metastasis, while a single mass may mislead the diagnosis of primary lung cancer as in our cases. Despite all these described radiological, serological, and clinical findings, histopathological evaluation is often required for diagnosis in isolated IgG4-RRD patients for the management and treatment of the disease.

Since IgG4-RD is a rare disease, a standard treatment scheme for the disease has not yet occurred. Based on the case series in the literature, systemic corticosteroid therapy is recommended as the first option in treatment (18). Response to corticosteroid treatment is generally good, and it is recommended to review the diagnosis in patients who do not receive an apparent response to treatment. Also, publications are reporting that rituximab therapy is beneficial in some cases (19).

In conclusion, IgG4-RRD is a rare disease with many diseases in its differential diagnosis. Isolated IgG4-RRD is rarely seen and is available in the literature as case reports. IgG4-RRD, which can make lung involvement in different patterns, rarely appears with mass-like lesions. Still, IgG4-RRD must be considered in the differential diagnosis of mass lesions detected in CCT. Laboratory, radiological, and histopathological findings of the disease should be evaluated together for an accurate diagnosis.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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