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Case and Review

IgG4-Related Pseudotumors Mimicking Metastases in Liver and Lungs

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Keywords

IgG4-related disease · Lymphadenopathy · Metastasis · Pseudotumor · Eosinophilic infiltration

Abstract

A 47-year-old man complained intermittent dull pain at the right upper quadrant abdomen and right neck swelling for 3 months. Blood tests revealed leukocytosis with mild eosinophilia. Computed tomography (CT) showed the presence of multiple nodules in the liver and both lung fields. Positron emission tomography/CT (PET/CT) scans found increased uptake at lymph nodes of the right neck, in the lung, liver, and prostate. The patient was diagnosed with IgG4-related disease (IgG4-RD) based on the biopsy findings from the right neck lymph nodes, showing enriched IgG4-positive lymphoplasmacytic cells. It is often difficult to distinguish IgG4-RD from malignancy, especially in presentations with multiple pseudotumors. This case serves as a reminder that IgG4-RD should be considered in earlier diagnosis, since pseudotumors in multiple organs may imitate tumor metastases.

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Introduction

IgG4-RD is a fibrous-inflammatory process that often involves multiple organs including cervical lymph nodes, lung, liver, pancreas, kidney, prostate, and salivary gland [1]. Three major pathological characteristics are distinguished: dense IgG4-positive lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. Eosinophilic infiltration may also be present [1]. This novel concept has been fully discussed due to its ambiguous manifestation. Tumor-like masses can be disseminated in the affected organs, mimicking metastases. Herein, we displayed a rare case of IgG4-RD presenting as multiple inflammatory pseudotumors involving the lungs and liver simultaneously. Clinical, radiological, and pathological outcomes of the patient were analyzed and the patient was successfully treated with corticosteroid and rituximab therapy without other medications.

Case Report

A 47-year-old man with complaints of right upper quadrant abdominal pain and right neck swelling lasting for 3 months was referred to our hospital. He had unremarkable medical or family history and no disease associated allergy, nor contact and travel history. Physical examination showed a 1.7×1.5 cm²-lymph node mass in the right neck at the carotid triangle with non-tender texture. Serum laboratory tests indicated leukocytosis (12,840/mm³, normal range: 4,000–10,000/mm³) with mild eosinophilia (eosinophils count: 821 cells/μL, normal range: 0–450 cells/μL) and an elevated IgG level (1,786 mg/dL, normal range: 635–1,741 mg/dL). Stool examination revealed no parasitic infections. Microorganisms were absent in Gomori Methenamine-Silver, Periodic Acid-Schiff, and Acid-Fast staining. In addition, we found no elevated levels of tumor markers like CEA, CA-199, and AFP. Abdominal sonography revealed hypoechoic multiple liver masses. Computed tomography (CT) scans showed multiple hypo-attenuation nodules of sizes up to 31 mm in the liver and both lungs with early enhanced and washed out (Fig. 1). Therefore, malignancy with multiple nodules disseminated throughout solid organs was suspected. No lesion was found under duodenoscopy and colonoscopy. Positron emission tomography (PET)/CT indicated various FDG-avid organs with SUVmax in neck lymph node: 4.9; lung: 1.4; liver: 5.3; prostate: 6.8 (Fig. 1). Percutaneous fine-needle biopsy of the liver showed necrotized granuloma, and transrectal needle biopsy of the prostate showed nodular hyperplasia. Both specimens were infiltrated with abundant eosinophils, but with no abnormal changes in the IgG4/IgG ratio. Histopathological approach via extensive excision of lymph nodes on the right neck showed a marked increase in the number of IgG4-positive plasma cells (>100 cells/HPF with IgG4+/IgG+ ratio of 80%) (Fig. 2).

Based on the histology grading of increased IgG4 positive plasma cells and high IgG4/IgG ratio in lymph nodes, IgG4-RD was suspected. The serum IgG4 level was then measured (2,080 mg/dL, normal range: 8–140 mg/dL). Treatment was subsequently applied with rituximab and methylprednisolone pulse therapy. Three weeks later, the patient responded by drops in both IgG levels (IgG: 1,538 cells/μL, IgG4: 1,630 cells/μL) and eosinophil counts (170

cells/ μ L). Three months later, follow-up CT showed regressive changes of pseudotumors at the liver and lung. The patient remains in a relapse-free condition so far.

Discussion

Clinical presentations of IgG4-RD have its occurrence at characteristics of certain organs, and may resemble malignant tumors or infections [2]. Patients usually have subacute enlarged tumefactive masses, which contribute to the general symptoms in or around the affected organs. In the present case, abdominal pain might well be related to the gastrointestinal and biliary tract. In more severe cases, patients may suffer from severe complications like obstructive jaundice due to hepatic, biliary, and pancreatic lesions [1]. Another symptom of IgG4-related lymphadenopathy is frequently its asymptomatic presentation, along with other clinical or laboratory findings [3]. Large cohort studies reported IgG4-related lymphadenopathy affecting 30–60% of those IgG4-RD patients [4–6]. IgG4-related lymphadenopathy is referred as the initial or one of the earliest manifestations of IgG4-RD [3]. However, the diagnosis of IgG4-RD based on lymph node biopsy is problematic because lymph nodes may not show fibrosis to the extent seen in organs [2]. Therefore, lymphadenopathy appears a sign for an early caution in the differential diagnosis of IgG4-RD, but the possibility of infectious diseases should be excluded in advance.

Nodular lesions on CT dubbed as inflammatory pseudotumors may interfere with the correct differential diagnosis. We reviewed current literatures discussing IgG4-related multiple pseudotumors involvement [7–12], and discovered that the confusing metastatic-like appearance in the initial CT images were often the misleading reason for these reports (Table 1). PET/CT was not implemented in single case because they got final results depending on organ biopsies, fortunately. However, it may come to a paradoxical end if pathology shows non-specific findings. For IgG4-RD, PET/CT is useful in detecting the disease activity and determining the extent of organ involvement [13]. As shown in Figure 1, the range of SUVmax accumulated by FDG is often highly-overlapped between IgG4-RD and malignancy (1.1–8.3 for IgG4-RD [14]; 2.99–24.09 for malignancy [15]), making their differential diagnosis challenging. PET/CT does not give good specificity for IgG4-RD, but it does provide information on the extent of organ involvement and for determining the proper sites for biopsy. Generally, inflammatory pseudotumors exist most commonly in the lung, and sporadically in extrapulmonary organs [16]. Even though approximately 60% of patients with IgG4-RD have multiorgan involvements [17], less case study reveals the concomitant presence of pulmonary and hepatic pseudotumors. In our case, pseudotumors found in lungs and liver intangibly supported the initial assumption of malignancy metastasis. This assumption was later altered by the unexpected pathological findings at the lymph nodes.

On the other hand, eosinophilia and eosinophilic infiltrations were observed in organs of our patient. The degree of eosinophilic infiltrations in tissues affected by IgG4-RD is typically mild to moderate in most cases; however, eosinophilic organopathy can be found in some extreme cases [2, 18]. Mohapatra et al. [19] reported that peripheral eosinophilia increases with rising IgG4 levels, and this adds diagnostic value at higher levels of serum IgG4. In our case,

eosinophilic infiltration was concurrently treated well after corticosteroid therapy. This implied that in IgG4-RD, the early eosinophilic infiltration in other organs could be resolved through an initial steroid therapy. This strategy of treatment has not been proposed before. Therefore, we suggested that biopsies should be carried out as much as possible in the event that eosinophilic infiltration is observed in only one of the involved organs, but with strong suspicion of IgG4-RD.

Conclusion

In conclusion, this is the first case of IgG4-RD with multiple pseudotumors reported in Taiwan. Multiple tumefactive nodules in two organs have misled us initially in the attempt to trace the origin of metastasis. In cases of IgG4-RD, PET/CT can give clues for appropriate situations of biopsies. Besides, often eosinophilic infiltration might be the only pathological presentation in the involved organs and that can be treated with corticosteroids. Consequently, IgG4-RD deserves greater awareness for its early diagnosis, and thus helps in preventing serious dysfunction of organs, irreversible tissue fibrosis, and overtreatment. This case points out a potential diagnostic pitfall and is worth the attention of physicians.

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Statement of Ethics

The authors confirm that the parents of the patient have given their written informed consent to publish the case report as well as pictures and tables.

Conflict of Interest Statement

The authors declared that they have no conflicts of interest.

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Author Contributions

Yueh H.Z. and Tung K.K. were accountable for study conception and design, acquisition of data, and writing the original draft; Yueh H.Z., Tung K.K., and Wen M.C. analyzed and interpreted the data; Tung C.F. provided the resources for the data and the methodology and validation of the case; Wen M.C. and Tung C.F. were supervisors for this draft; Yueh H.Z. and Tung K.K. reviewed and edited the draft. All authors have read and approved the final manuscript.

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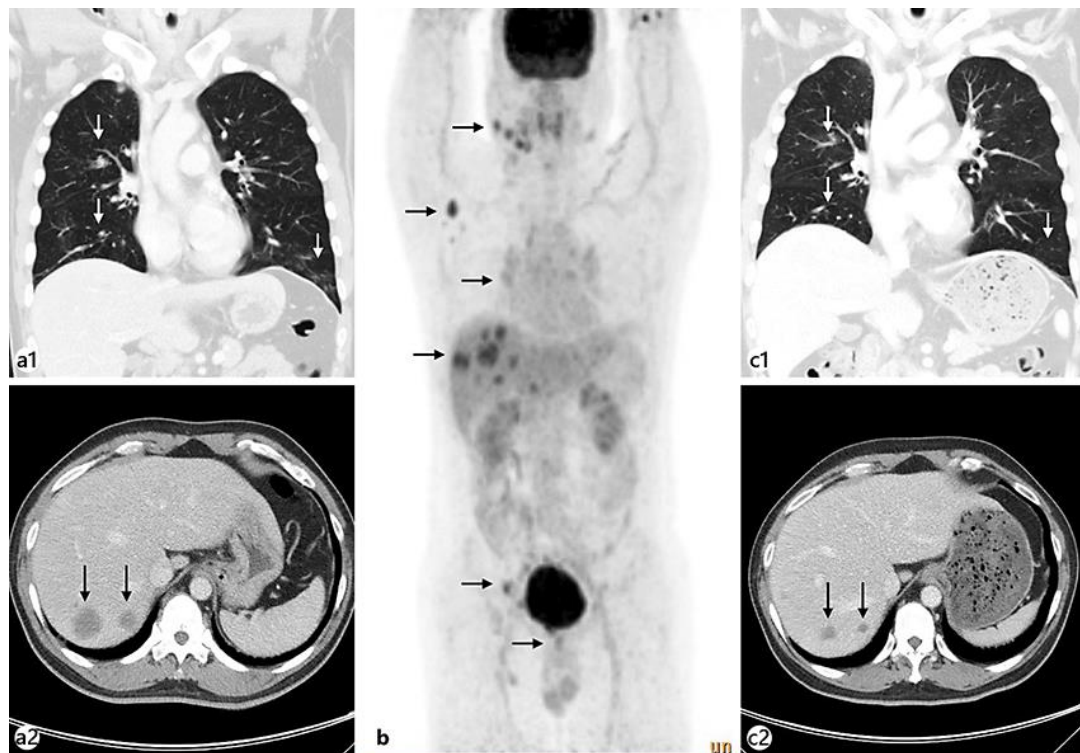


Fig. 1. Liver and lung pseudotumors before and after the treatment. **a1/a2** CT scans showing pre-treatment multiple hypoattenuation nodules of sizes up to 31 mm in the liver and both lungs. **b** PET/CT revealing elevated levels of FDG uptake in the liver, prostate, right anterior pelvic regions, right neck, both lungs, mediastinum, and pulmonary hilar regions on both sides. **c1/c2** Regressive changes of the liver and lung pseudotumors after treatment for 3 months.

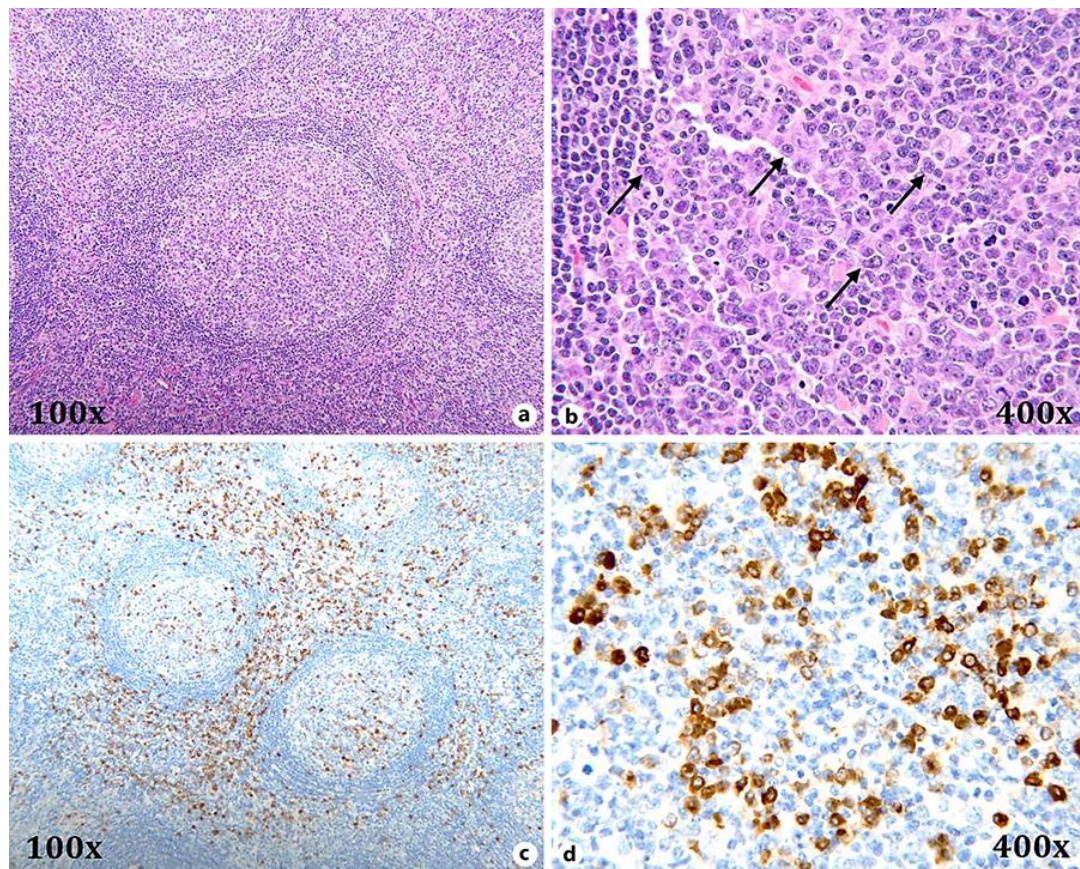


Fig. 2. Pathological images of the lymph nodes. **a** 100× and **b** 400× hematoxylin and eosin (H&E) staining of the lymph node showing abundant presence of plasma cells (arrows) infiltrating the follicular and interfollicular areas. Note the absence of malignant cells. **c** 100× and **d** 400× of IgG pathologic marker. Note the abundant presence of IgG4-positive plasma cells (>100 cells/HPF with IgG4+ to IgG+ ratio of 80%) in the interfollicular region.

Table 1. Comparison of recent cases of IgG4-related multiple organ involvement

First author	Symptom	Year	Age/ sex	IgG4 level (mg/dL), IgG4/IgG ratio	Size, cm	Location	Biopsy
Cases of IgG4-related multiple inflammatory pseudotumors in the literature							
Surintranont J, [7]	Hematuria	2019	52/M	NM, 54%	8.5	Liver, kidney, both lungs	Liver, kidney
Higashioka K, [8]	Swelling of submandibular gland	2015	64/M	2,750, 90%	NM	Submandibular, parotid, lacrimal gland, mediastinum, lung, inguinal lymph node, spleen, aorta, jejunum	Kidney, inguinal lymph nodes
Okano A, [9]	Visual disturbance, quad- rantanopia of the right eye	2015	62/M	405, NM	NM	Masses near the right paraclinoid at the right Meckel's cave and along the left fora- men magnum	Right paraclinoid
Nishino T, [10]	Headache, occasional left- sided facial numbness	2013	67/M	3,410, 100%	NM	Dural-based mass lesions in the bilateral Sylvian fissures, bilateral enlargement of the lachrymal glands and parotid glands	Parotid gland, kidney
Dias OM, [11]	Dyspnea and fatigue	2011	70/M	936, 90%	NM	Pulmonary nodules with ground glass halo in the middle lobe	Lung
Tsuboi H, [12]	Fever, fatigue, anorexia and arthralgia	2011	62/M	292, 23%	NM	Pituitary stalk, lungs, retroperitoneum	Lung
Current case	Abdominal pain	2019	47/M	1,786, 80%	3.1	Lymph nodes, lungs, liver, prostate	Lymph nodes, liver, prostate

The diagnostic criteria for IgG4-RD including: (A) an increased serum IgG4 concentration ≥ 135 mg/dL; (B) histological appearance: ratio of IgG4/IgG-positive cells > 40% and IgG4-positive cell count > 10/HPF; (C) localized/diffuse tumefactive masses in single/multiple organs[1].