Case Report

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대한영상의학회지

Immunoglobulin G4-Related Disease of the Ovary Mimicking Bilateral Ovarian Malignancies

양측 난소의 악성 종양으로 오인한 난소의 면역글로불린 G4 관련 질환

Yongsik Sim, MD[1], Taek Chung, MD[2], Dae Chul Jung, MD[1]*, Hyun-Soo Kim, MD[2], Young Taik Oh, MD[1]

Departments of [1]Radiology, [2]Pathology, Yonsei University College of Medicine, Seoul, Korea

Immunoglobulin G4-related disease (IgG4-RD) is a fibro-inflammatory condition characterized by several pathological features that can theoretically involve all organs. Ovarian involvement in IgG4-RD has been reported by two studies only. Herein, we report a pathologically confirmed case of ovarian involvement of IgG4-RD, which mimicked bilateral ovarian malignancies on computed tomography and magnetic resonance imaging.

Index terms Immunoglobulin G; Autoimmune Diseases; Female; Computed Tomography, X-Ray; Magnetic Resonance Imaging

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***Corresponding author**
Dae Chul Jung, MD
Department of Radiology,
Yonsei University
College of Medicine,
50-1 Yonsei-ro, Seodaemun-gu,
Seoul 03722, Korea.

Tel 82-2-2228-7400
Fax 82-2-2227-8337
E-mail DAECHUL@yuhs.ac

ORCID iDs
Yongsik Sim
https://orcid.org/0000-0003-2711-2793
Taek Chung
https://orcid.org/0000-0001-7567-0680
Dae Chul Jung
https://orcid.org/0000-0001-5769-5083
Hyun-Soo Kim
https://orcid.org/0000-0002-2356-7822
Young Taik Oh
https://orcid.org/0000-0002-4438-8890

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized fibro-inflammatory condition that is characterized by several pathological features (1). Although elevated serum IgG4 concentration has been reported to be associated with IgG4-RD and to have modestly high sensitivity and specificity (2-4), pathologic tissue confirmation remains the ultimate gold standard for diagnosing IgG4-RD. IgG4-RD has been reported in various organs including pancreas, liver, bile duct, lung, pleura, kidney, aorta, lymph node, lacrimal gland, salivary gland, skin, paranasal sinus (5). Within the scope of our investigation, however, only two recent publications have described ovarian involvement of IgG4-RD (6, 7). Herein, we report a case of rare ovarian involvement of IgG4-RD with literature review.

CASE REPORT

A 53-year-old woman presented to the gynecology department for one month of persistent abdominal pain. She had no significant medical history other than dyslipidemia. An initial abdominopelvic computed tomography (CT) scan revealed solid, oval-shaped, poorly enhancing mass-like enlargement of bilateral ovaries (Fig. 1A). The left ovary measured 6.3 cm × 4.1 cm and the right one measured 5.4 cm × 3.7 cm. Multiple conglomerated precaval and paraaortic lymph nodes measuring up to 2.4 cm in the longest diameter were also noted (Fig. 1A). T2-weighted magnetic resonance (MR) images showed high signal intensity of internal stroma and relatively low signal intensity of the peripheral portion of both ovaries, while T1-weighted images showed homogeneously isointense to slightly hyperintense signal intensity of the ovaries compared to that of the myometrium (Fig. 1B). Gadolinium contrast-enhanced T1-weighted images demonstrated subtle enhancement in the peripheral portion of the ovaries where the T2 signal intensity was relatively low (Fig. 1B). Based on the CT and MRI, our differential diagnosis included bilateral ovarian metastases (Krukenberg tumor) and sex-cord stromal tumors such as granulosa cell tumor. Positron emission tomography-CT (PET-CT) demonstrated mild ^{18}F-fluorodeoxyglucose (FDG) uptake in bilateral ovaries [standardized uptake values (SUV): 2.5 and 2.4, left and right, respectively] and intense ^{18}F-FDG uptake in the left paraaortic lymph node (SUV: 4.14) (Fig. 1C). None of serum tumor markers was reported to be elevated; cancer antigen (CA)-125 17.6 (U/mL), human epididymis protein 4 40.9 (pmol/L), carcinoembryonic antigen 1.19 (ng/mL), CA 19-9 21.6 (U/mL) and alpha-fetoprotein < 0.5 (ng/mL). The serum IgG4 level was not measured.

She underwent an elective exploratory laparoscopy. About 5 cm × 5 cm sized left, and right ovarian masses were noted (Fig. 1D) in the pelvic cavity. The excised ovaries weighed 39 g and 30 g, left and right, respectively. Bilateral salpingo-oophorectomy was performed. Benign stromal tumors were reported in the frozen section of both ovaries. The final pathologic evaluation reported lymphoid follicular hyperplasia with dense plasmacytic infiltration involving bilateral ovaries and paratubal tissue (Fig. 1E). Additional immunohistochemistry using monoclonal antibodies against IgG and IgG4 was performed (Fig. 1F). The estimated IgG-positive plasma cell count was 240 per high-power field (HPF), IgG4-positive plasma cell count was 120/HPF and the calculated IgG4-positive to IgG-positive plasma cell ratio was 50%. Unlike other organs, the cutoff value of IgG-positive plasma cell count for the diagnosis of ovarian IgG4-RD has not been proposed yet. Nonetheless, the pathology result of the patient fulfilled at least one of three major pathological features and mandatory IgG4-positive to IgG-positive plasma cell ratio of 40%. In addition, the number of IgG4-positive cells per HPF exceeded the reference values of most organs (10, 30, 50 or 100/HPF) except for the reference value proposed for skin (200/HPF). Through the multidisciplinary discussion of gynecologists, radiologists and pathologists, other possible diagnoses were excluded and the collaborated diagnosis of IgG4-RD was adopted. Within a few days, the patient was discharged without complication. At the first follow-up two months later, the patient had no symptom and ultrasonography was unremarkable. The clinician decided not to add any treatment and planned another follow-up schedule a year later.

Fig. 1. A 53-year-old woman diagnosed with IgG4-related disease involving both ovaries.
A. Axial contrast-enhanced CT images demonstrate oval-shaped, poorly enhancing solid mass-like enlargement of both ovaries (left, arrowheads). The left ovary measures 6.3 cm × 4.1 cm and the right one measures 5.4 cm × 3.7 cm. The average post-contrast attenuation numbers of left and right ovaries are 34.9 HU and 37.7 HU respectively, which were 22.7 HU and 23.9 HU on pre-contrast CT scans (not shown). Several enlarged and conglomerated lymph nodes are noted in paraaortic and aortocaval space (right). The largest node, situated at the level of mid kidney measures 2.4 cm in the longest diameter (arrow). Contrast enhancement of the enlarged lymph nodes appears homogeneous and there is no evidence of internal necrosis.
B. T1WI (left) shows homogeneously isointense to slightly hyperintense signal intensity of the right ovary compared to that of the myometrium (arrow). T2WI (middle) shows high signal intensity of the internal stroma of the ovary and relatively low signal intensity of the peripheral portion (arrow). Gadolinium CET1 (right) shows subtle enhancement in the peripheral portion of the right ovary, where the T2 signal intensity is relatively low (arrow). The left ovary is not included in the same plane.
C. PET-CT scans demonstrate mild ^{18}F-FDG uptake in both ovaries (SUVs were 2.5 and 2.4 for the left (thick arrow) and right ovaries (arrowhead), respectively). An enlarged left paraaortic lymph node shows intense ^{18}F-FDG uptake (SUV: 4.14) (arrows). No other abnormal ^{18}F-FDG uptake is observed in the scanned abdomen and pelvis.
D. Bilaterally enlarged ovaries (approximately 5 cm × 5 cm) are observed during exploratory laparoscopy.
CET1 = contrast-enhanced T1WI, FDG = fluorodeoxyglucose, HU = Hounsfield unit, IgG4 = Immunoglobulin G4, SUV = standardized uptake value, T1WI = T1-weighted image, T2WI = T2-weighted image

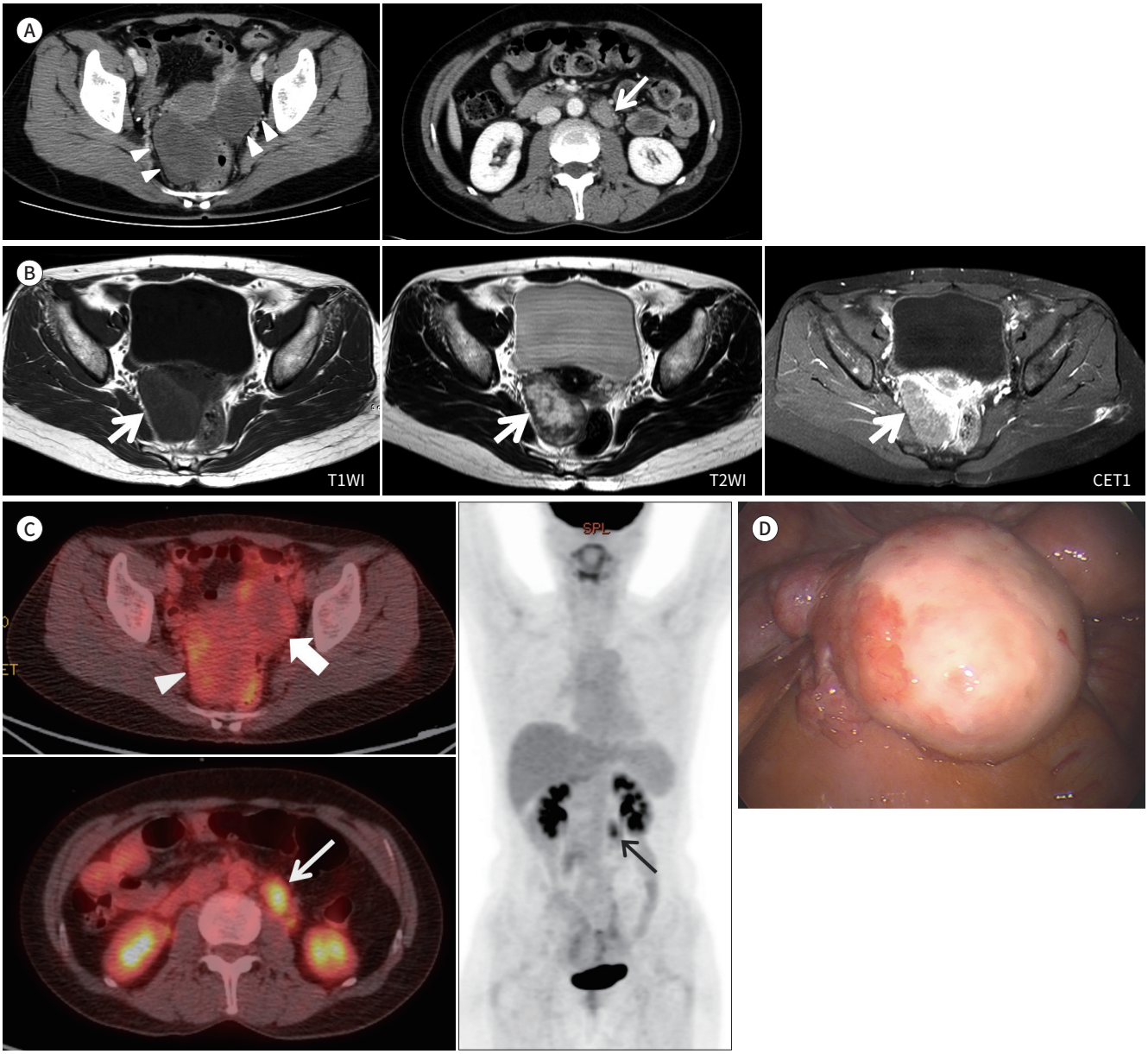
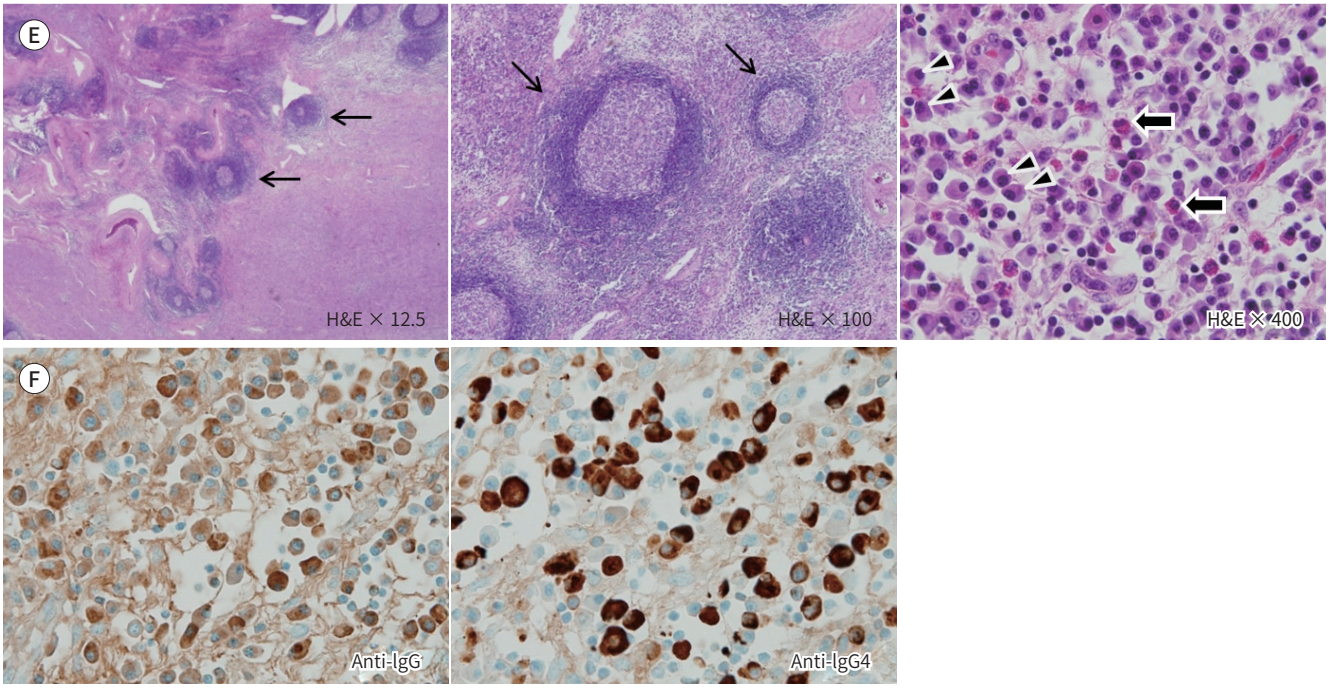


Fig. 1. A 53-year-old woman diagnosed with IgG4-related disease involving both ovaries.
E. H&E stained sections of ovarian tissue (left: × 12.5, middle: × 100, right: × 400) demonstrate lymphoid follicular hyperplasia (arrows) with dense plasmacytic infiltration (plasma cells are indicated by arrowheads) with a few eosinophils (thick arrows).
F. Immunohistochemistry with anti- IgG and IgG4 monoclonal antibodies reveals IgG-positive (240/HPF) (left) and IgG4-positive plasma cells (120/HPF) (right).
IgG = Immunoglobulin G, H&E = hematoxylin and eosin, HPF = high-power field



DISCUSSION

IgG4-RD a fibro-inflammatory condition that is characterized by several pathological features and theoretically capable of involving any organ. According to the consensus statement on the pathology of IgG4-RD by Deshpande et al. (1), the diagnosis of IgG4-RD requires collaborated pathological and clinical investigations. To establish a histopathological diagnosis of IgG4-RD, not only at least one of three major histopathological features; 1) dense lymphoplasmacytic infiltrates, 2) fibrosis arranged at least focally in a storiform pattern, 3) obliterative phlebitis, but increased IgG4-positive plasma cell count (or an increased ratio of IgG-positive cell to IgG4-positive cell count) in biopsied or excised tissue should be fulfilled (5). If any two of the three major criteria are met and the number of IgG4 positive cells exceeds the cutoff value with an IgG4(+)/IgG(+) ratio over 40%, the top-tiered diagnosis of "Histologically highly suggestive of IgG4-RD" can be suggested. The proposed cutoff values differ by organs, ranging from 10/HPF (meninges and liver) to 200/HPF (skin). Also, the lacrimal gland requires only one major criterion as an exception. The second tier diagnosis called "probable histological features of IgG4-RD" consists of cases presented by a single criterion, cases of inconclusive pathology obtained by needle biopsy and cases involving organs with limited published data (i.e. meningeal and cutaneous disease). To confirm the diagnosis of these "probable" cases of IgG4-RD, additional clinical, radiological or serological findings such as elevated serum IgG4 level above 135 mg/dL or involvement of other organs should be demonstrated.

In order to recognize the ovary as a new involvement site of IgG4-related disease, it is necessary to meet stricter criteria according to the consensus statement; 1) characteristic histopathological findings with an elevated IgG4-positive plasma cells and IgG4-to-IgG ratio, 2) high serum IgG4 concentrations, 3) effective response to glucocorticoid therapy, 4) other organ involvement that is consistent with IgG4-related disease. Maruyama et al. (6) recently reported a case of IgG4-RD involving bilateral ovaries which met all of three typical histopathologic features, while Sekulic et al. (7) reported a case of IgG4-RD involving left ovary which met two of the three major histopathologic features (dense lymphoplasmacytic infiltrates and obliterative phlebitis) of the IgG4-RD (Table 1). In the case of Maruyama et al. (6), serum IgG4 level was above 1000 mg/dL to meet the second criterion. On the other hand, serum IgG4 levels were not reported in the case of Sekulic et al. (7) and in our case. However, Maruyama et al. (6) somehow reported the number of infiltrating lymphoplasmacytic cells (300/HPF) instead of estimating IgG-positive cells, which made their case insufficient to meet the required criteria. Other organ involvement as the fourth criterion was assumed in Maruyama's case (mesenteric nodules and lymph nodes) and in our case (paraaortic lymph nodes). Above all, none of the reported cases was initiated with glucocorticoid therapy and the response to glucocorticoid has never been evaluated. Thus far, there are limited evidence to declare the ovary as a new involvement site of IgG4-RD. However, the spectrum of IgG4-RD has been expanding and the ovary is likely to be considered a new involvement site in the near future. Radiologically, the case of Maruyama et al. (6) showed a 14 cm multinodular pelvic mass with mesenteric nodules on MRI mimicking ovarian malignancy, while the case of Sekulic et al. (7) revealed nor-

Table 1. Characteristics of Reported Cases of IgG4-Related Disease Involving the Ovary

References	Patient Age	Radiologic Features	Major Histopathologic Features	IgG4+Count, IgG+/IgG4+Ratio	Serum IgG4 Level	Response to Glucocorticoid	Other Organ Involvement
Maruyama et al. (6) (2016)	59	Multinodular solid mass (14 cm) • T1WI: homogeneously low SI • T2WI: heterogeneous SI • CE-T1WI: diffuse contrast enhancement	3/3 (lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis)	Does not meet criteria	1000 mg/dL	Not tried	Mesenteric nodules, lymph nodes
Sekulic et al. (7) (2017)	47	Normal sized ovaries	2/3 (lymphoplasmacytic infiltration and obliterative phlebitis)	40–50/HPF, 40–50%	Not measured	Not tried	None
Current case	53	Enlarged bilateral ovaries (6.5 cm, 5.1 cm) • T1WI: homogeneously isointense • T2WI: heterogeneous SI • CE-T1WI: subtle peripheral contrast enhancement	1/3 (lymphoplasmacytic infiltration)	120/HPF, 50%	Not measured	Not tried	Paraaortic lymph nodes

CE = contrast enhanced, HPF = high-power field, IgG4 = Immunoglobulin G4, SI = signal intensity, T1WI = T1-weighted image, T2WI = T2-weighted image

mal-sized ovaries. Our case has shown bilateral ovarian enlargement with paraaortic lymphadenopathy.

In conclusion, we reported a rare case of IgG4-RD involving bilateral ovaries diagnosed by an interdisciplinary approach. In our opinion, the ovary needs to be investigated as a new site of IgG4-RD involvement, despite limited documentation. The acceptable cutoff value of IgG4-positive plasma cell count for the ovary should also be carefully estimated. Radiologically, IgG4-RD of the ovary may mimic bilateral ovarian malignancy on CT and MRI due to its solid nature and potential for associated lymphadenopathy.

Author Contributions

Conceptualization, all authors; data curation, all authors; formal analysis, all authors; funding acquisition, J.D.C.; investigation, all authors; methodology, all authors; project administration, S.Y., J.D.C.; resources, all authors; software, S.Y., J.D.C.; supervision, S.Y., J.D.C.; validation, all authors; visualization, S.Y., C.T., J.D.C.; writing—original draft, S.Y., C.T., J.D.C.; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25:1181-1192
2. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis* 2015;74:14-18
3. Yu KH, Chan TM, Tsai PH, Chen CH, Chang PY. Diagnostic performance of serum IgG4 levels in patients with IgG4-related disease. *Medicine (Baltimore)* 2015;94:e1707
4. Hao M, Liu M, Fan G, Yang X, Li J. Diagnostic value of serum IgG4 for IgG4-related disease: a PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)* 2016;95:e3785
5. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol* 2010;34:1812-1819
6. Maruyama S, Sato Y, Taga A, Emoto I, Shirase T, Haga H. Immunoglobulin G4-related disease presenting as bilateral ovarian masses and mimicking advanced ovarian cancer. *J Obstet Gynaecol Res* 2016;42:103-108
7. Sekulic M, Pichler Sekulic S, Movahedi-Lankarani S. IgG4-related disease of the ovary: a first description. *Int J Gynecol Pathol* 2017;36:190-194

대한영상의학회지

양측 난소의 악성 종양으로 오인한 난소의 면역글로불린 G4 관련 질환

심용식[1] · 정 택[2] · 정대철[1]* · 김현수[2] · 오영택[1]

면역글로불린 G4 관련 질환은 신체 전 장기를 침범할 수 있는 전신적인 섬유-염증성 질환이다. 면역글로불린 G4 관련 질환이 난소를 침범한 경우는 드물어서 현재까지 2건의 증례만이 보고되었다. 컴퓨터단층촬영 및 자기공명영상에서 양측 난소의 악성 종양으로 오인되었으나 병리학적으로 면역글로불린 G4 관련 질환으로 진단한 증례를 보고하고자 한다.

연세대학교 의과대학 [1]영상의학교실, [2]병리학교실