American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e926803
DOI: 10.12659/AJCR.926803

Received: 2020.06.14
Accepted: 2020.09.05
Available online: 2020.09.17
Published: 2020.10.27

A 47-Year-Old Woman with Immunoglobulin G4 (IgG4)-Related Disease Involving the Right Ovary

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 47-year-old
Final Diagnosis: IgG4-related disease
Symptoms: Ovarian cyst • pelvic mass
Medication: —
Clinical Procedure: —
Specialty: Obstetrics and Gynecology • Pathology

Objective: Rare disease

Background: Immunoglobulin G4 (IgG4)-related disease is immune-mediated and was first proposed as a defined entity after studies on patients with autoimmune pancreatitis. Since then, it has been reported in many organs. Involvement of the ovaries is rare, and to our knowledge, only 2 cases have been reported in the literature. IgG4-related disease is associated with increased serum IgG4 levels. Organ involvement includes a lymphoplasmacytic infiltrate, fibrosis, and obliterative phlebitis, with immunohistochemistry showing IgG4-positive plasma cells. This report is of a case of IgG4-related disease involving the right ovary.

Case Report: A 47-year-old woman presented with a right ovarian cyst. An ultrasound scan revealed a complex right ovarian cyst with multiple septations. The hormonal profile and tumor markers were unremarkable. Gross examination showed fragments of cyst wall. Histologic examination revealed a follicular cyst, surrounded by a dense lymphoplasmacytic infiltrate rich in eosinophils, partially obliterative phlebitis, and fibrosis. Immunohistochemically, IgG marked most of the plasma cells, of which 70% expressed IgG4, with a count >50 cells per high-power field. Subsequent testing of serum IgG4 showed that the level was elevated (330 mg/dL). A diagnosis of IgG4-related disease was made.

Conclusions: Ovarian involvement by IgG4-related disease is rarely described in the literature. Our patient is likely to be the third case. We believe that cumulative findings from our case along with the 2 already reported cases increase awareness and may establish a framework for building more objective criteria to define this entity in the ovaries, similar to what has been achieved in some other organs.

MeSH Keywords: Fibrosis • Immunoglobulin G • Ovary • Phlebitis • Plasma Cells

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/926803

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Background

Immunoglobulin G4 (IgG4)-related disease, which is immune-mediated, was first described in 2003 by Kamisawa et al. after a study describing an association between a subtype of autoimmune pancreatitis and other systemic autoimmune diseases [1]. Although it is still unclear whether the role of the IgG4 molecule is primary or secondary in the disease process of such conditions [2], the association of these conditions with IgG4 was first known in 2001, when it was found that patients with sclerosing pancreatitis have a higher plasma concentration of IgG4 [3]. Subsequently, the pancreatic and extrapancreatic fibroinflammatory lesions were found to be rich in IgG4-positive plasma cells [1,4].

IgG4-related disease now has been described in virtually every organ system and similar histopathologic features are seen, with minor variation in some organs [5]. The main histopathologic features are dense lymphoplasmacytic infiltrate, fibrosis with storiform pattern at least focally, and obliterative phlebitis [4]. In general terms, the diagnosis of IgG4-related disease requires measurement of increased serum levels of IgG4 with histologic findings of organ involvement by a lymphoplasmacytic infiltrate, fibrosis, and obliterative phlebitis and immunohistochemistry that shows predominance of IgG4-positive plasma cells in the infiltrate [4–7]. Unlike some other organs, no specific criteria were established for involvement of the ovaries, given the rarity of this presentation.

To our knowledge, IgG4-related disease involving the ovaries has been reported only twice in the literature [8,9]. The presentation varied between the 2 cases as 1 patient, similar to the patient in our case, presented with an ovarian mass suspicious for malignancy [8] and the other case was an incidental finding in a patient who had undergone a total abdominal hysterectomy with salpingo-oophorectomy performed as part of management for leiomyoma [9]. The present report is of a case of IgG4-related disease involving the right ovary.

Case Report

A 47-year-old woman was referred to our hospital outpatient clinic after she was found to have a complex right ovarian cyst. A comprehensive clinical history was taken from the patient. Her medical history was unremarkable and her surgical history was significant only for a partial gastrectomy for obesity and a myomectomy, 1 year and 4 years prior to her current presentation, respectively. Transvaginal ultrasonography revealed no abnormalities in the uterus, the right adnexa showed a 5.0×4.0 cm complex ovarian cyst with septations, and the left adnexa showed a 2.0×2.0 cm simple cyst.

At presentation, the patient was medically well with normal vital signs. The complete blood count (CBC) showed a hemoglobin level of 10.2 g/dL with features suggestive of iron deficiency anemia, while the white blood cell (WBC) count, and the differential and platelet counts were within normal limits. Urinalysis was unremarkable. The patient's hormonal profile (estradiol, follicle-stimulating hormone, luteinizing hormone, inhibin, and testosterone) was unremarkable. Tumor markers were within normal limits.

A laparoscopic right salpingo-oophorectomy subsequently was performed and biopsies were taken from the omentum, left ovary, and endometrium. The remainder of the left ovary was left in place to supply endogenous hormones. The patient's postoperative serum IgG4 level was 330 mg/dL.

The right ovary was received in the pathology laboratory as fragmented pieces of a cystic structure aggregating to 7.5×6.0×2.0 cm. Representative sections were routinely processed, and slides were stained with hematoxylin and eosin. Microscopic evaluation of the right ovary revealed fragments of follicular cyst, surrounded by a dense lymphoplasmacytic infiltrate with numerous eosinophils (Figure 1). The inflammatory cell infiltrate was observed in all tissue fragments. Foci of fibrosis were identified (Figure 1A, 1B). In some areas, the lymphoplasmacytic infiltrate involved the walls of veins (phlebitis) to the extent of almost replacing the lumen in some of them in obliterative fashion (Figure 1C, 1D). Immunohistochemical studies for CD138, IgG, and IgG4 (Figure 2) showed a significant number of plasma cells in the infiltrate (Figure 2A), with most of them expressing IgG (Figure 2B). Approximately 70% of the latter group expressed IgG4 and these IgG4-positive cells were numerous to the extent of >50 cells per high-power field in some foci (Figure 2C, 2D). The included fallopian tube showed no significant inflammation. Periodic acid-Schiff (PAS) staining was performed on the right ovarian tissue and showed no growth of fungal organisms. There was no morphologic evidence of malignancy. Histologic examination of the specimen from biopsy of the left ovary showed a corpus luteum cyst with no significant inflammation. Examination of the specimens from biopsies of the omentum and endometrium was unremarkable. Based on the combination of histologic features, immunohistochemical finding of a significant number of IgG4-positive plasma cells in the examined right ovarian tissue, and the elevated serum level of IgG4, a diagnosis of IgG4-related disease of the ovary was made. The patient was followed up shortly after her surgery and discharge. Because she was satisfied that malignancy had been excluded, she did not return for further follow-up at our hospital. However, she was contacted and reported an unremarkable clinical course.

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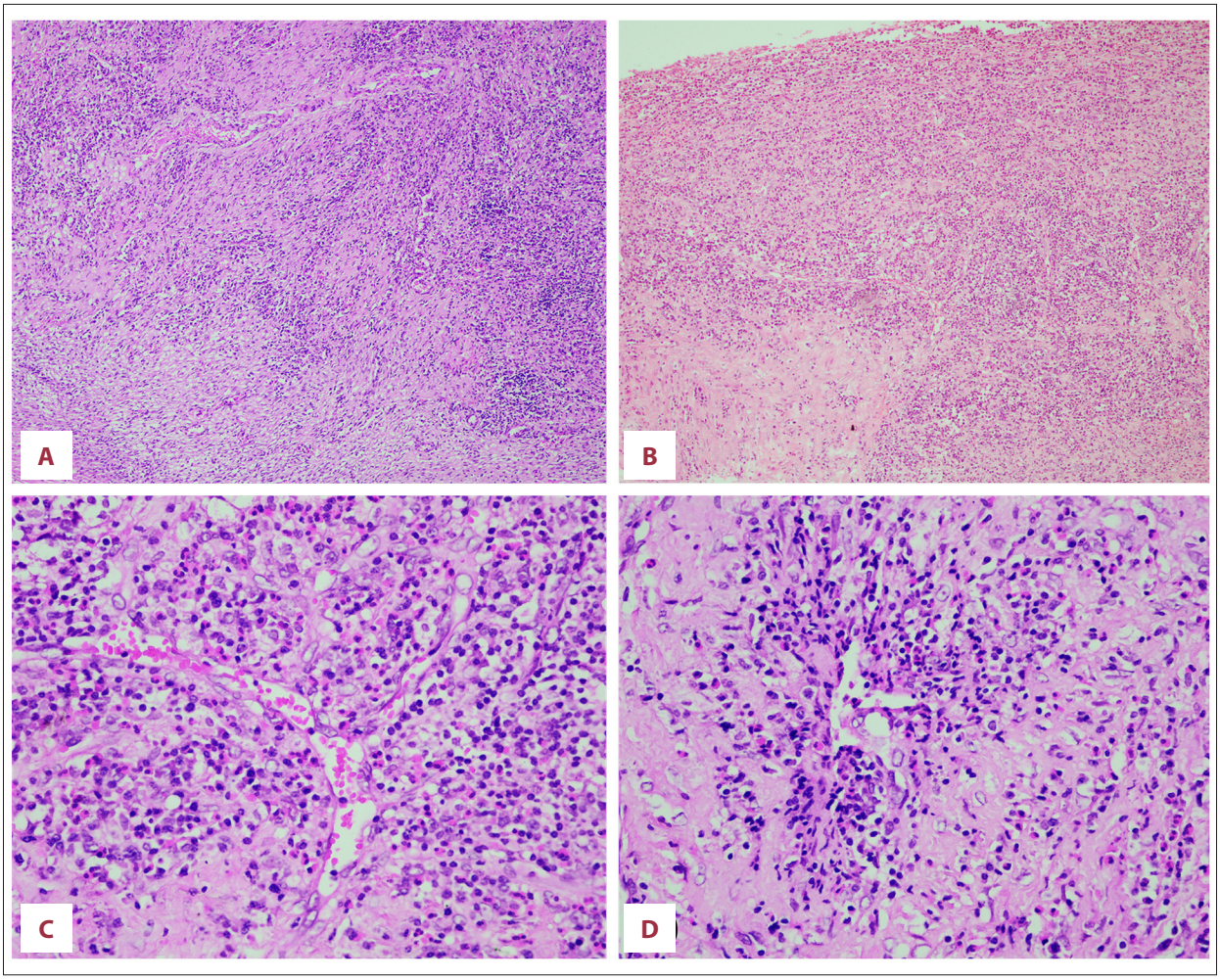

Figure 1. Main histologic features (hematoxylin and eosin staining). (**A**) Diffuse lymphoplasmacytic inflammatory cell infiltrate in the ovary with areas of fibrosis (original magnification 100×). The infiltrate is angiocentric, as is apparent in the 2 vessels shown. (**B**) Original magnification 100×. In a high-power view, the infiltrate appears rich in plasma cells and eosinophils and there is accentuation around veins with involvement of the wall (phlebitis) and extension into the lumen with obliteration. (**C, D**) Original magnification 400×.

Discussion

In the patient described here, morphologic features of eosinophil-rich lymphoplasmacytic infiltrate alongside the fibrosis and obliterative phlebitis prompted us to evaluate the nature of the plasma cell infiltrate. Immunohistochemical analysis of these plasma cells showed that many of them were IgG-positive; the majority expressed the IgG4 molecule. These findings suggested the diagnosis of IgG4-related disease of the ovary. The ultrasonographic suspicion of malignancy was excluded histologically. With the patient having an otherwise unremarkable systemic medical history before and after her presentation and being thoroughly examined by the clinical team during her stay at the hospital, there were no features to suggest infectious processes or systemic diseases.

Given the diverse organ systems that are involved by IgG4-related disease, a consensus statement with the goal of standardizing and establishing agreed-upon criteria to diagnose IgG4-related diseases was formulated in Boston, Massachusetts, United States in 2011. The authors stressed the centrality of morphology in establishing this diagnosis, supported by the demonstration of IgG4-positive plasma cells [4]. According to that statement, the major histologic features that are required for diagnosis are a dense lymphoplasmacytic infiltrate distributed diffusely throughout the lesion, storiform fibrosis, and venous obliteration by the dense inflammatory infiltrate. Those findings were demonstrated in the present case, although the fibrosis was not obviously storiform. However, according to the literature on IgG4-related disease, the latter feature was not present in all organs diagnosed with the disease. For example, fibrosis is not necessary for diagnosis

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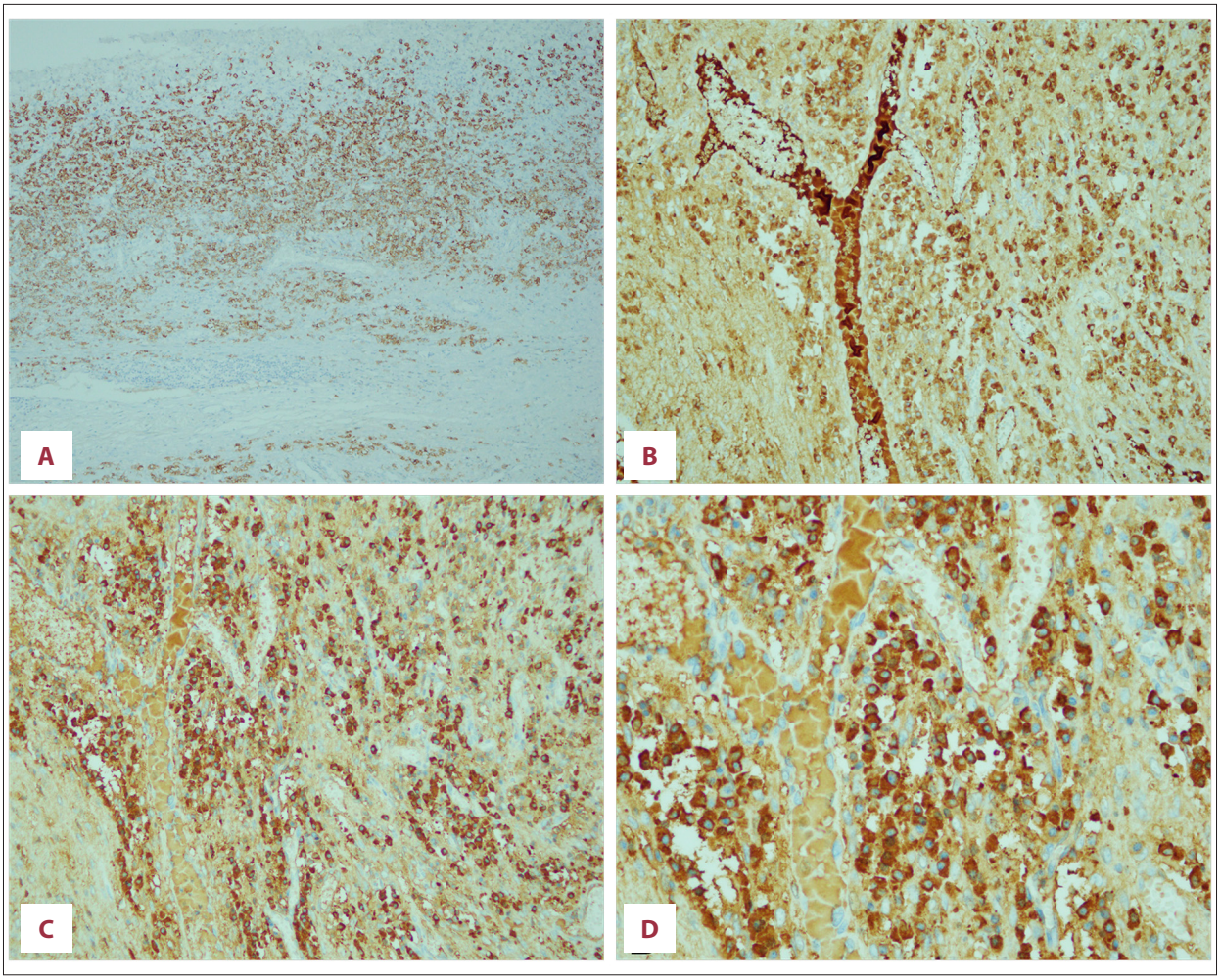

Figure 2. Immunohistochemical characteristics of the plasma cell infiltrate. (**A**) A CD138 marker highlights the prominent plasma cell component of the inflammatory infiltrate (original magnification 100×). (**B**) Most of the plasma cells show expression of immunoglobulin G (IgG) (original magnification 200×). (**C**) An IgG4 marker shows that more than 70% of the IgG-positive plasma cells express IgG4 (original magnification 200×). (**D**) In a high-power view, the number of plasma cells expressing IgG4 is in excess of 50 cells per high-power field (original magnification 400×). The findings in **C** and **D** reflect an increased number of IgG4-positive plasma cells beyond the cut-off value for the diagnosis of IgG4-related disease.

of the disease in lacrimal or salivary glands or the lung [4]. Moreover, 1 of the 2 previously described patients with ovarian IgG4-related disease had no significant fibrosis (whether storiform or not) [9]. The inflammatory infiltrate in our patient also was rich in eosinophils, a feature that is described in the consensus as 1 of the associated features, albeit it is not major [4]. Quantification of IgG4-positive plasma cells in the lesion also is a major part of the diagnosis, because IgG4-positive cells also can be found in infiltrates that are not specific for this entity. Two parameters can be used for quantification: the number of IgG4-positive cells per high-power field and the IgG4/IgG ratio. The required number of IgG4-positive cells per high-power field might vary, depending on the organ and the degree of fibrosis, but more than 10 IgG4-positive cells per high-power field was proposed for use as part of the comprehensive diagnostic criteria. The IgG4/IgG ratio is a more robust and specific tool for establishing the diagnosis and a cut-off value greater than 40% was proposed for this purpose [4]. In our case, both of these parameters were met with more than 50 IgG4-positive plasma cells per high-power field and an IgG4/IgG ratio of approximately 70%.

Although elevated serum IgG4 is present in the majority of patients, the fact that about 30% of patients with histopathologic features of IgG4-related disease have a normal value make its sensitivity and utility as a diagnostic tool of less importance [5–7]. Nevertheless, the finding of an elevated serum IgG4 level can further boost the diagnosis when the relevant histopathologic criteria are met, as in the case presented here, in which the serum IgG4 level was 330 mg/dL.

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Because the ovary is an organ in which involvement by IgG4-related disease previously has not been described, our case must fulfill the minimum consensus requirements. They are: 1) characteristic histopathologic findings; 2) high serum IgG4 concentration; 3) effective response to glucocorticoids; and 4) reports of other organ involvement by the same process [4,6]. In our case, it was not possible to meet criteria 3 and 4 because our patient did not want to seek further treatment or investigations, as her concern was only to exclude a malignant process. Nevertheless, the consensus group took into account the difficulties that come when studying a new entity or an entity in new sites and stated that appropriate histopathologic findings with only 1 additional requirement are sufficient [4,6]. The second minimal requirement (high serum IgG4 level) was met in our case.

Two cases of IgG4-related disease involving the ovaries have been reported in the literature [8,9]. One, which was reported by Maruyama et al., had a presentation similar to our case, with an ovarian mass mimicking a malignant process [8], while the second case was an incidental finding after a total abdominal hysterectomy and bilateral salpingo-oophorectomy for symptoms related to leiomyoma [9]. Compared with our case, however, the first case relied mainly on the percent of IgG4-positive plasma cells in relation to the total number of lymphocytes and plasma cells in the inflammatory infiltrate to establish the diagnosis, a method which was criticized by Sekulic et al., who reported the second case, for not being a diagnostic component of the Boston consensus statement criteria. In the second case, there was no significant fibrosis and serum IgG4 testing was not performed.

The clinical differential diagnosis of the present case was mainly of a malignant ovarian cyst, which was excluded based on histologic examination. The histologic differential diagnosis of lymphoplasmacytic infiltrate can include a chronic oophoritis in the setting of pelvic inflammatory disease (PID) and lymphoplasmacytic lymphoma. Significant acute inflammation, foamy histiocytes. and granulomatous inflammation were lacking in our case. In addition, the asymptomatic clinical presentation and other clinical findings do not support PID-associated chronic oophoritis. Primary lymphoplasmacytic lymphoma of the ovary is rare [10], and histologic features include a denser lymphoplasmacytic infiltrate than in our case. An increased number of eosinophils is not a feature, similar to the fibrosis and vascular obliterative lesions found in our case. Another possible histologic differential diagnosis of this case is eosinophilic perifolliculitis, another rare entity described twice in the literature [11,12]. However, phlebitis and appreciable fibrosis are not reported features of the latter entity. Furthermore, IgG4 assessment of plasma cells was not conducted in these 2 cases. Therefore, our case is more consistent with IgG4-related disease.

Conclusions

Ovarian involvement by IgG4-related disease is rarely described in the literature. Our patient is likely to be the third case. We believe that cumulative findings from our case along with the 2 previously reported cases increase awareness and may establish a framework for building more objective criteria to define this entity in the ovary, similar to what has been achieved in some other organs.

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Conflicts of interest

None.

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