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IgG4-related disease in the pelvis: A mimicker of gynecologic malignancy

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ABSTRACT

This report describes a unique case of IgG4-related disease in a 36-year-old woman who presented with a pelvic mass. Although CT and MR imaging initially suggested a malignant process, further work-up including sigmoidoscopy and surgical exploration revealed no evidence of malignancy. The final pathology indicated an inflammatory process, leading to the diagnosis of IgG4-related disease. After receiving appropriate systemic treatment, the patient's symptoms significantly improved. This case underscores the limitations of current imaging studies and emphasizes the importance of considering a wide range of potential diagnoses when dealing with pelvic masses of uncertain etiology.

1. Introduction

Due to its diagnostic complexity, IgG4-related disease (IgG4-RD) is often underdiagnosed and can be mistaken for malignancy. When patients present with mass formation, this disease is frequently confused with cancer and will often be treated as such (Nambiar and Oliver, 2024). This case is one of the few that describes IgG4-RD mimicking a gynecologic malignancy. Early recognition and treatment of IgG4-RD can prevent significant disease-related complications and limit inappropriate treatment in cases of misdiagnosis. Correct diagnosis is crucial in preventing organ damage, end-stage organ failure, debilitating tissue fibrosis, unnecessary surgery, and in some cases, death (Kamisawa et al., 2015). Fortunately, IgG4-RD is highly treatable and shows a favorable response to systemic corticosteroid treatment. Therefore, IgG4-RD should be included in the differential diagnosis for patients presenting with pelvic masses, particularly in cases with discordant tissue pathology (Lanzillotta et al., 2020).

2. Case

A 36-year-old nulliparous female presented to the emergency room with three months of worsening pelvic pain and constipation. CT imaging of the abdomen and pelvis revealed an irregular soft tissue mass measuring up to 6.5 cm located posterior to the right adnexa and adjacent to the uterus. Imaging also indicated rectal wall thickening and enlarged perirectal and pelvic lymph nodes. Findings were described as most consistent with a primary rectal cancer. The patient's gynecologic history was notable for high-grade cervical dysplasia with positive high-risk HPV co-testing and was negative for sexually transmitted infections, pelvic inflammatory disease, endometriosis, or chronic pelvic pain. Due to clinical concerns for impending large bowel obstruction, the patient was transferred to a tertiary care center to accommodate consultation with colorectal surgery.

Continued workup in the hospital included flexible sigmoidoscopy, which noted extrinsic compression of the rectal wall. While the rectal mucosa appeared edematous on endoscopy, findings were negative for any intraluminal pathology. Following the endoscopy, a pelvic MRI was ordered. Findings demonstrated a large pelvic mass involving the right broad ligament and right pelvic sidewall. The MRI also confirmed the presence of suspected metastatic adenopathy previously noted on CT imaging. Considering the negative endoscopic findings, the mass was described as having multifocal perirectal invasion of a non-gastrointestinal origin, favoring a lesion originating from within the uterus, cervix, or ovary (Fig. 1). Gynecologic and GI-related tumor markers were normal. After return of bowel function with an aggressive bowel regimen, the patient was discharged home and outpatient consultation with gynecologic oncology was arranged.

During office consultation, a pelvic exam was notable for a normal appearing vagina and cervix, and bimanual and rectovaginal exams were consistent with MRI findings. An exam under anesthesia was scheduled to obtain a core tissue biopsy of the palpable mass. On bimanual examination, there was a firm, immobile 8 cm mass filling the

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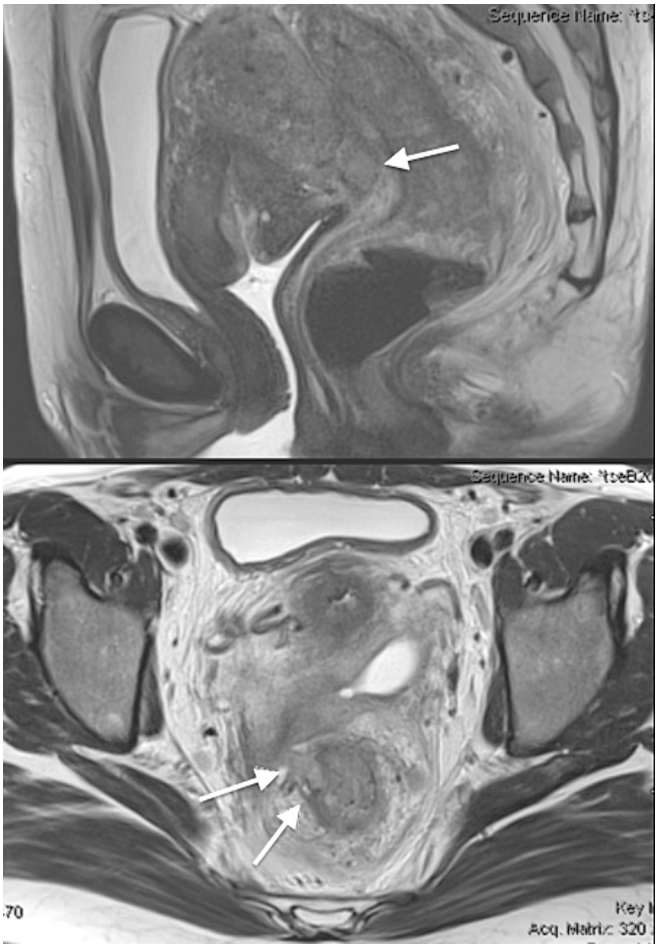

Fig. 1. T2 weighted pelvic MRI images. The top image shows the primary pelvic mass (denoted with a single solid arrow) with proximity to the posterior uterine body and posterior vaginal fornix. The bottom image denotes an additional, smaller soft tissue mass with appreciable perirectal infiltration (demarcated by two solid arrows).

posterior pelvic cul-de-sac, and the parametria were clear. Multiple core biopsies were obtained transvaginally, and the patient recovered appropriately from the procedure. The final pathologic assessment was negative for malignancy and most consistent with inflammation as assessed by a gynecologic pathologist.

Given the discordance between the patient's clinical presentation, examination, and imaging findings with a strong suspicion for malignancy, it was determined that further surgical management would best assist in diagnosis and treatment. The patient strongly desired fertility-sparing management if feasible. The patient subsequently underwent abdominal exploration including right salpingo-oophorectomy, right pelvic and paraaortic lymph node biopsies, and rectal mesentery biopsy. Intra-operative findings revealed a circumferential solid tumor surrounding the rectosigmoid colon with localized induration. The right pelvic and paraaortic lymph nodes were enlarged and sampled. The right adnexal structures were densely adherent to the right pelvic sidewall, uterus, and rectum, although there were no characteristic features of ovarian cancer. A right-sided hydroureter was identified extending to the level of the pelvic brim. After adhesiolysis, the right ovary and fallopian tube were removed for pathologic assessment. The rectal mesentery was significantly thickened and inflamed, and this area was also biopsied. On further abdominal survey, all other peritoneal surfaces including the upper abdomen were normal. There was no definitively malignant disease present in the abdomen or pelvis.

All specimens were sent for intraoperative frozen pathology assessment and returned negative for evidence of malignancy. Specifically, pathologic evaluation of the right ovary showed ovarian stroma with adherent smooth muscle and inflammation. The differential diagnosis included oophoritis, tuboovarian abscess, and salpingitis, without any concern for malignancy. The right pelvic lymph node biopsy showed follicular lymphoid hyperplasia, and the rectal mesentery biopsy showed spindle cell proliferation with inflammatory cells. Given these inconclusive findings, attempt at complete resection of the mass was aborted.

Post-operatively, the patient was scheduled to follow up with an infectious disease specialist. Targeted infectious work up included bacterial and fungal antigens and cultures, which were all negative. All surgical specimens were reviewed by a gynecologic pathologist and confirmed to be negative for malignancy and infection. Final pathology favored inflammatory changes with findings of lymphoplasmacytic infiltrate, salpingitis, serositis, and tubo-ovarian adhesions. The right ovary showed ovarian stroma with sclerosis and a marked mixed acute and chronic lymphoplasmacytic infiltrate (Fig. 2). The case was presented at the Multidisciplinary Gynecologic Oncology tumor board, and the findings were felt to be most consistent with chronic autoimmune oophoritis. Immunohistochemical evaluation showed ovarian stroma with markedly increased IgG staining for lymphocytes, of which a significant fraction stained positive with IgG4, with a significantly elevated IgG4/IgG ratio. Therefore, this best supported the presence of IgG4-RD (Fig. 3).

Serum immunoglobulin levels were obtained to evaluate for plasma cell dyscrasias and IgG4-RD. Serologic testing resulted with IgG level of 1577 mg/dL (normal range 635–1741 mg/dL) and IgG4 level of 216 mg/dL (normal range 2–96 mg/dL), confirming the diagnosis of IgG4-RD. Ultimately, the patient established with rheumatology, and after initiating a high-potency oral corticosteroid, she experienced complete resolution of her symptoms and a decrease in size of her pelvic mass on clinical exam.

3. Discussion

This case highlights the clinical complexity of an autoimmune and inflammatory disorder known as IgG4-RD. IgG4-RD encompasses a spectrum of diseases characterized by elevated levels of serum IgG4 and infiltration of affected tissues by IgG4-positive plasma cells, which often leads to mass formation. This condition can manifest in various organ systems, most commonly involving the pancreas, retroperitoneum, salivary glands, and kidneys (Nambiar and Oliver, 2024; Stone et al., 2012). Although the exact cause of this disease is still unknown, there have recently been advancements in the understanding of its immunopathogenesis, diagnostic complexities, and therapeutic approaches.

The diagnostic criteria for IgG4-RD have been updated to include a combination of clinical, serological, and histopathological findings (Umehara et al., 2021). The current criteria for diagnosing IgG4-RD are based on one or more organs with a characteristic mass, nodule, or swelling (either diffuse or localized), an elevated serum IgG4 concentration (>135 mg/dL), and a histopathological diagnosis of tissue fibrosis. The pathologic appearance of IgG4-RD is specifically characterized by storiform fibrosis or obliterative phlebitis and elevated levels of IgG4-producing plasma cells within dense lymphoplasmacytic infiltrate (Umehara et al., 2021).

It is important to understand that while an elevated serum IgG4 level is necessary for diagnosis, this is not pathognomonic of IgG4-RD. Several types of cancer can also yield increased IgG4 plasma levels, making it difficult to differentiate between malignancy and IgG4-RD (Fox and Fox, 2014). As a result, histopathological evaluation continues to be the most reliable method of diagnosis (Sodavarapu et al., 2020). As detailed in the reported case, malignancy remained at the top of the differential diagnosis until surgical pathology was comprehensively assessed by an expert gynecologic pathologist. Therefore, treatment of suspected malignancy should not be initiated without a definitive pathologic

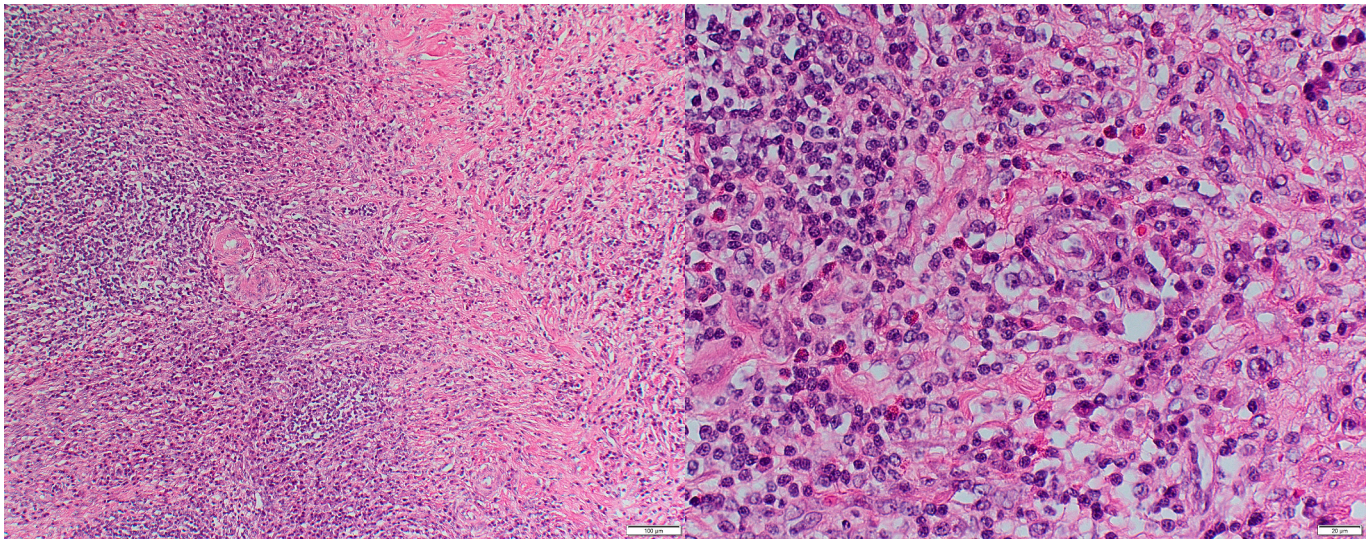

Fig. 2. Histologic features of the right ovary on H&E stain at (a) low power (100× magnification), left, and (b) high power (400× magnification), right. Images show ovarian stroma with sclerosis and a marked mixed acute and chronic lymphoplasmacytic infiltrate.

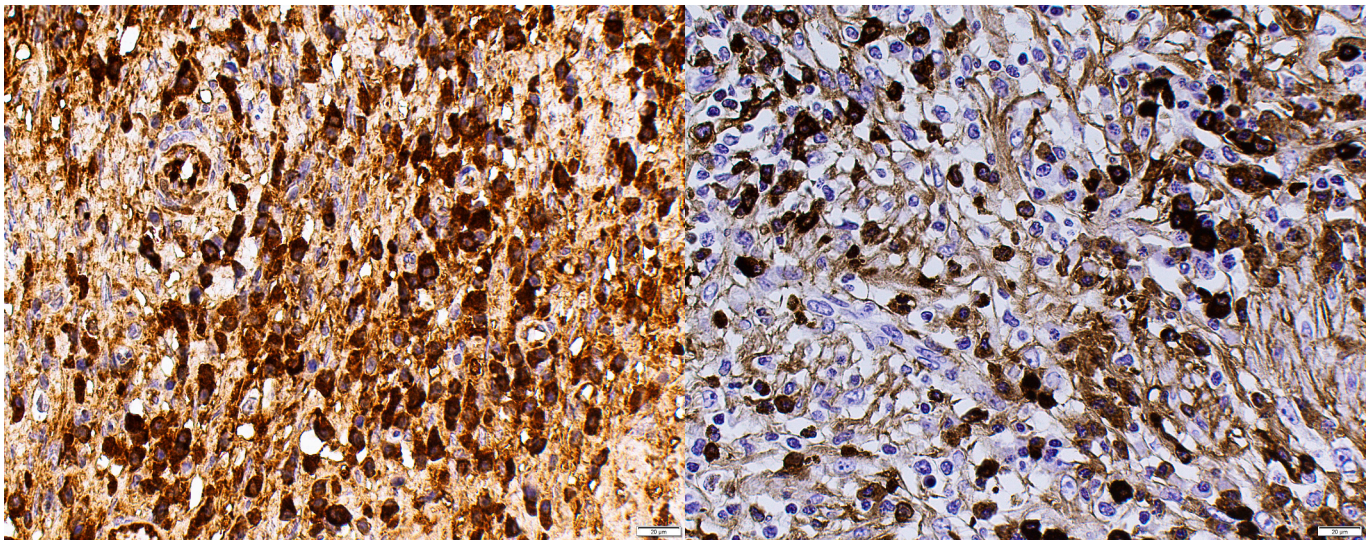

Fig. 3. Immunostains performed on the right ovary at high power (400× magnification) for (a) IgG, left, and (b) IgG4, right. Images show ovarian stroma with markedly increased IgG staining for lymphocytes, a significant fraction of which stain positive with IgG4, with a significantly elevated IgG4/IgG ratio over 40%.

diagnosis.

Imaging studies such as MRI can be instrumental in identifying inflammatory changes typical of IgG4-RD. Additionally, PET-CT can be considered to distinguish IgG4-RD from malignancy based on patterns of metabolic activity. These diagnostic tools can collectively aid in accurate diagnosis and inform appropriate treatment approaches in many cases (Zheng et al., 2020). For the case presented, the presence of enlarged pelvic lymph nodes on CT and MRI favored metastatic lymphadenopathy. Since the intent of surgical intervention was to provide a tissue diagnosis, a PET-CT was not utilized to assess for distant disease pre-operatively. If utilized, this imaging modality may have been instrumental in triaging this patient to a benign etiology for her disease.

While IgG4-RD most commonly manifests in salivary, pancreatic, or retroperitoneal tissues, some studies have described IgG4-RD involving gynecologic organs. Although these cases are rare, reports of IgG4-RD affecting the ovaries, uterus, and vagina have been documented (Akyol et al., 2021; Pacyna et al., 2023; Rujiwetpongstorn et al., 2022). In each of these cases, at least two of the three diagnostic criteria for IgG4-RD were met. One report details two patients presenting with IgG4-RD masquerading as uterine and cervical cancers, with key factors contributing to a delayed IgG4-RD diagnosis (Pacyna et al., 2023). For example, one patient with biopsy-proven cervical cancer and hypermetabolic retroperitoneal lymph nodes had persistent nodal FDG avidity following chemoradiotherapy. Pathological analysis of the nodal tissue was negative for malignancy but notable for significant levels of IgG4-plasma cells. Upon initiation of systemic steroids, this patient experienced significant clinical improvement (Pacyna et al., 2023). Another case reviewed a patient with vaginal IgG4-RD who was inappropriately treated for vulvovaginal cancer. Unfortunately, this patient suffered adverse treatment-related events associated with her cancer therapy and died (Rujiwetpongstorn et al., 2022). These cases highlight the importance of definitive pathologic diagnosis before initiating malignancy-directed treatment.

This case is a rare example of IgG4-RD mimicking gynecologic malignancy in the posterior pelvic cul-de-sac. Few previous case reports have reviewed IgG4-RD misdiagnosed as cervical, ovarian, and vaginal malignancies. This case illuminates the limitations of contemporary imaging studies, such as CT and MRI. Early recognition and treatment of

IgG4-RD is critical to prevent significant disease- and treatment-related complications. The disease is commonly mislabeled as cancer, and patients have subsequently received unnecessary treatment for malignancy in some cases. It is crucial to consider IgG4-RD as a diagnosis for patients presenting with pelvic masses, especially in cases with discrepant pathology results. Importantly, this condition is highly treatable, and patients can experience complete resolution with systemic corticosteroid treatment.

Consent statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRediT authorship contribution statement

Kristen Stearns: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Binathi Vuppuluri:** Writing – original draft. **Ruth Lininger:** Writing – review & editing. **Laurel K. Berry:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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