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Case report

IgG4-related disease mimicking gynecologic malignancy

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ABSTRACT

Immunoglobulin G4 (IgG4) related disease is a systemic disease that causes fibrosis, tumor-like nodules, and lymphoid hyperplasia with infiltration of IgG4 positive plasma cells. It can manifest in many organ systems; however, there are few cases that report gynecologic organ involvement. It is crucial to correctly diagnose IgG4-related disease versus malignancy because the former is treated with glucocorticoids or rituximab. In this case report, we describe two patients in which IgG4-related disease mimics gynecologic cancer. In the first case, an 85 year old woman presented with diffuse lymphadenopathy and a uterine mass concerning for malignancy. Biopsies were negative for carcinoma. Inguinal lymph node biopsy demonstrated IgG4 positive plasma cells and the patient was treated with rituximab therapy given concurrent severe rheumatoid arthritis. In the second case, a 35 year old woman under surveillance for Stage IB2 squamous cell carcinoma of the cervix (status post definitive chemoradiation therapy) presented with fluorodeoxyglucose (FDG) avid paraaortic lymph nodes on positron emission tomography (PET) imaging with subsequent negative paraaortic lymph node biopsies. Serial imaging and biopsies remained inconclusive despite ongoing diffuse lymphadenopathy and clinical concern for recurrence. Supraclavicular lymph node excision was performed which demonstrated lymphoid hyperplasia with increased IgG4 plasma cells and no evidence of carcinoma, supporting the diagnosis of IgG4-related disease. The patient was treated with high dose steroids with clinical improvement and resolution of abnormal imaging findings. We demonstrate that IgG4-related disease can present with FDG-avid lesions on PET imaging and lymphadenopathy that mimics primary or recurrent gynecologic malignancy. While rare, we conclude the IgG4-related disease is an important differential diagnosis to consider in the workup of primary or recurrent gynecologic malignancy and highlights the value of PET imaging to identify unusual patterns of lymphadenopathy and guide histologic confirmation of disease.

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated disease that was first described by Hamano et al. in 2001, and it is characterized by systemic fibrosis, tumor-like nodules, and lymphoid hyperplasia (Hamano et al., 2001). A defining feature is the presence of dense lymphoplasmacytic infiltrations with immunoglobulin G4 (IgG4) positive plasma cells in affected tissues. IgG4-RD is under-recognized and therefore the exact prevalence is unknown. IgG4-RD has been described in many organ systems, however, there are few cases that report gynecologic organ involvement. In such cases, IgG4-RD has been shown to mimic gynecologic malignancy in ovarian (Akyol et al., 2020; Maruyama et al., 2016; Michaud Maturana et al., 2019), uterine (Ohkubo et al., 2015; Senda et al., 2021), and cervical tissues (Mizuno et al., 2016). It is crucial to recognize and distinguish IgG4-RD from gynecologic malignancy because the former is treated with glucocorticoids and/or rituximab with good response (Maritati et al., 2020; Samji et al., 2020). We present two cases in which IgG4-RD mimicked primary metastatic uterine and recurrent cervical carcinomas. Informed consent was obtained and documented from both patients.

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2. Case report 1: Primary uterine mass with diffuse lymphadenopathy

An 81 year old woman (gravida 0) with past medical history of nonspecific joint pain presented with unintentional weight loss and anemia for eight months. Computed tomography (CT) scan demonstrated a 6 × 5 cm heterogenous uterine mass with poorly defined endometrium as well as retroperitoneal and axillary lymphadenopathy (Fig. 1A–C). Positron emission tomography (PET) showed mild heterogenous fluorodeoxyglucose (FDG) uptake (standardized uptake value (SUV) 2.6) within the uterine mass and hypermetabolic lymph nodes including pelvic, bilateral inguinal, and bilateral axillary nodes (Fig. 1D–F). Overall, these findings raised concern for possible uterine malignancy with metastasis for which she was referred for gynecologic oncology evaluation. She denied any pelvic symptoms and pelvic exam was normal without palpable masses. Colonoscopy and mammogram were normal. Endometrial biopsy showed benign tissue, and fine needle aspiration of the right axillary lymph node was negative for malignant cells. Based on the location and the patient's desire to avoid major surgery, transrectal myometrial uterine biopsy was performed which was also negative for carcinoma. The uterine mass was suspected to be a benign fibroid, however definitive diagnostic options were discussed with the patient including hysterectomy to which she declined and opted for continual observation. Repeat PET showed interval worsening of hypermetabolic left pelvic and inguinal lymph nodes without other significant changes from prior exams. Ultrasound-guided core needle biopsy of the left inguinal lymph node was performed and demonstrated reactive hyperplasia with IgG4 positive plasma cells and no malignant cells (Fig. 3A–D).

The patient was referred to rheumatology and started on methylprednisolone 8 mg daily. During her rheumatologic evaluation, physical exam showed bilateral wrists with severely decreased range of motion, fusion, and possible rheumatoid nodules. Nodular changes were also noted in the bilateral metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints. The patient had significantly elevated serum inflammatory markers and elevated cycle citrullinated peptide IgG antibodies consistent with undiagnosed rheumatoid arthritis (RA). Serum IgG4 was also elevated to 204 mg/dL (normal: 2.4–121 mg/dL). Given the high likelihood of IgG4-RD and coexisting RA, the patient was transitioned from methylprednisolone to rituximab with continual follow-up.

3. Case report 2: Suspected recurrent cervical carcinoma

A 31 year old woman (gravida 0) presented with post-coital and inter-menstrual bleeding for six months. Pelvic exam was grossly normal with normal appearing cervix and no masses noted. Pap smear showed high grade squamous intraepithelial neoplasia. Colposcopy showed acetowhite lesions and mosaicism on the cervix with abnormal vessels noted. Cervical biopsy confirmed invasive, moderately differentiated squamous carcinoma, grade 2 or 3. Magnetic resonance imaging (MRI) around the time of diagnosis demonstrated a cervical mass measuring 4.2 × 4.2 × 3.5 cm abutting the rectum but without invasion to the rectum or the bladder. There was no regional adenopathy. Positron emission tomography (PET) showed a hypermetabolic cervical mass without other hypermetabolic lymph nodes or lesions. There was a left supraclavicular hypermetabolic region that was interpreted as probable muscle uptake with a recommendation to follow-up on exam. Overall findings were consistent with Stage IB2 squamous cell carcinoma of the cervix. The patient was treated with radio-sensitizing cisplatin and external beam radiation therapy followed by high dose rate brachytherapy. MRI prior to brachytherapy showed near complete resolution of the cervical mass with a small residual enhancing soft tissue nodule up to 1.2 cm at the anterior-inferior aspect of the cervix.

Three months later, post-treatment PET showed decreased intensity of the hypermetabolic focus in the cervix but hypermetabolic retroperitoneal lymph nodes raising suspicion for metastasis. The patient underwent exploratory laparotomy with *para*-aortic lymphadenectomy. Subsequent pathology was negative for carcinoma in five total *para*-aortic lymph nodes and one left common iliac lymph node and surveillance was advised. Two months later, she established care at our institution for surveillance and at that time endorsed an episode of heavy vaginal bleeding as well as persistent severe pelvic pain. Pelvic exam was limited by pain but notable for necrotic appearing tissue and parametrial tethering concerning for recurrent disease. Office biopsies showed necrosis and radiation atypia. Subsequent exam under anesthesia was performed with multiple superficial and deeper core cervical biopsies showing benign inflamed fibromuscular tissue with radiation

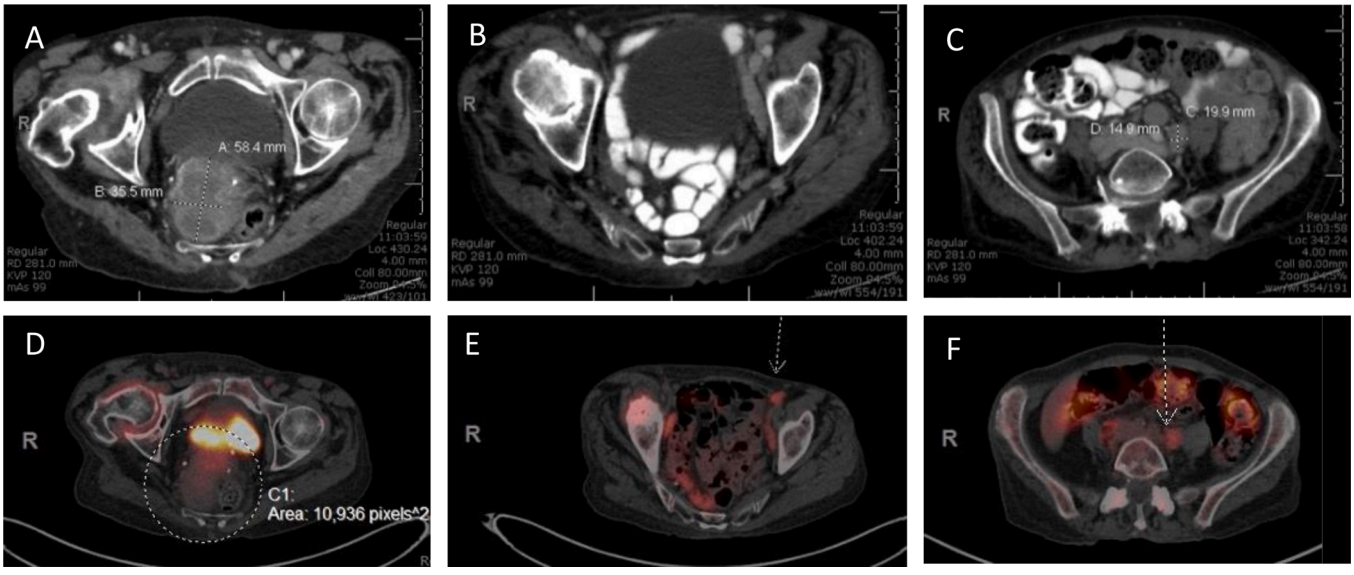

Fig. 1. Radiologic findings for case report 1, primary uterine mass with diffuse lymphadenopathy. (A) Axial CT showing heterogenous uterine mass measuring approximately 6 × 5 cm. (B) Axial CT showing prominent external iliac and inguinal lymph nodes. (C) Axial CT showing enlarged left common iliac lymph node measuring approximately 1.5 × 2 cm. (D) Axial PET/CT FDG showing heterogenous FDG uptake in the uterine mass and increased metabolic activity in the right hip. (E) Axial PET/CT FDG showing a hypermetabolic left external iliac lymph node. (F) Axial PET/CT FDG showing a hypermetabolic left common iliac lymph node.

induced atypia and no evidence of carcinoma. However, repeat PET demonstrated a hypermetabolic mass in the cervical/uterus region that was increasing in size from prior imaging as well as abnormally hypermetabolic retroperitoneal and left iliac lymph nodes (Fig. 2A, B). Of note, the left supraclavicular region of concern had increased in size and activity from prior imaging, suspicious for metastatic lymphadenopathy. MRI findings were consistent with PET, demonstrating diffuse nodular thickening of the cervical and parametrial regions with retroperitoneal and iliac lymphadenopathy. Altogether, these imaging findings were concerning for disease recurrence with metastatic spread.

Given the unclear clinical course with concern for disease progression on imaging and repeated negative biopsies, the left supraclavicular lymph node was excised to obtain definitive diagnosis. Pathology reported reactive hyperplasia with markedly increased IgG4 positive plasma cells and no evidence of carcinoma, suggesting IgG4-RD as the primary disease rather than cancer recurrence (Fig. 3E–H). Serum IgG4 was normal. The patient was referred to rheumatology and treated with a three week course of prednisone. At the six month follow-up visit, PET demonstrated an interval decrease in size and hypermetabolic activity of the pelvic mass and pelvic lymph nodes, with complete resolution of some nodal activity (Fig. 2C). As of her most recent follow-up, she was clinically without evidence of recurrent malignancy five years post-treatment completion.

4. Discussion

IgG4-RD is an immune-mediated systemic disease that can mimic other conditions including solid tumors and autoimmune diseases. Standardized diagnostic criteria for IgG4-RD was first proposed by Umehara et al. and include: (i) diffuse or focal enlargement of single or multiple organs; (ii) elevated serum IgG4 concentration (>135 mg/dl); and (iii) characteristic histopathological findings, including massive lymphoplasmacytic infiltration with fibrosis and an increased number of IgG4 + plasma cells (IgG4+/IgG + plasma cell ratio >40% and >10 IgG4 + plasma cells/high power field) (Maruyama et al., 2016; Umehara et al., 2012). However, these diagnostic criteria have been challenged, particularly with regard to serum IgG4 levels. Several studies have demonstrated that serum IgG4 concentrations are not always elevated, with one study showing that elevated serum IgG4 levels were present in just over half of patients with IgG4-RD confirmed from biopsy specimen (Stone et al., 2015). When evaluating clinical, serological, and histopathological features to diagnose IgG4-RD, biopsy-proven histopathological features is the strongest diagnostic consideration (Akyol et al., 2020; Maruyama et al., 2016). In the two cases we presented, one had mildly elevated serum IgG4 levels and the other had normal serum IgG4 concentrations demonstrating the decreased utility of this measure compared to histopathological features. Additionally, serum IgG4 levels are nonspecific and can be elevated in several other diseases (i.e., eosinophilic polyangiitis, interstitial lung disease, rheumatoid arthritis, systemic lupus erythematosus, etc.) (Stone et al., 2015). In general, IgG4-RD should be considered based on clinical suspicion (presence of tumor-like lesions in more than one organ), imaging findings (multiple nodules and enhancement patterns), and laboratory abnormalities (hypergammaglobulinemia, hypocomplementemia) when differentiating from gynecologic malignancies (Stone et al., 2015).

These two cases highlight important findings regarding IgG4-RD and gynecologic malignancies. First, we confirm previous reports that IgG4-RD can present as a uterine mass with diffuse lymphadenopathy (Ohkubo et al., 2015; Senda et al., 2021). In both previously published reports, uterine mass excision and hysterectomy were performed prior to histopathological evaluation and exclusion of malignancy. Hysterectomy was offered in this case but declined by the patient. Instead, diagnosis was eventually achieved through stepwise imaging and biopsies including ultrasound-guided inguinal lymph node biopsy. This conservative approach may have prevented unnecessary surgical complications and morbidity associated with performing hysterectomy in an elderly patient (Senda et al., 2021); however, this approach presents a trade-off between invasiveness and definitiveness of diagnostic procedures. In addition, this patient initially presented with nonspecific symptoms including weight loss, anemia, and had a history of nonspecific joint pain that was later diagnosed as severe untreated RA. A broad, systems-based differential with earlier recognition of joint manifestations and referral to rheumatology may have prevented unnecessary imaging and biopsies. In addition, earlier evaluation of serum inflammatory markers and/or immunoglobulin tests in patients with a uterine mass and diffuse lymphadenopathy could lead to earlier diagnosis.

In the second case, IgG4-RD mimicked recurrence of cervical carcinoma. To our knowledge, there is only one prior case that reports concurrent IgG4-RD and primary cervical carcinoma (Mizuno et al., 2016). We demonstrate that IgG4-RD can mimic progression of gynecologic disease after definitive initial treatment. Our case differs in that the initial evaluation and diagnosis of cervical carcinoma did not show signs of advanced disease or adenopathy. In addition, there was an adequate response to treatment characterized by near resolution of the cervical mass. During surveillance, clinical exam and presence of hypermetabolic nodes in the retroperitoneum led to concern for recurrence and disease spread. Several features in this case common to both IgG4-RD and disseminated malignancy are abdominal/pelvic pain as well as retroperitoneal and *para*-aortic lymphadenopathy (Hedgire et al., 2013). Another complicating factor was whether the patient's pain and bleeding was related to IgG4-RD, cancer recurrence, or post-radiation complications; thus, a broad differential is important to consider particularly prior to initiation of treatment for recurrent malignancy in atypical clinical circumstances. A large cohort study found that IgG4-RD is associated with malignancies, especially within the first year of diagnosis, and that some may consider IgG4-RD as a paraneoplastic syndrome; however, gynecologic malignancy was not one of the cancers identified in the study (Asano et al., 2015).

FDG PET/CT is utilized in both gynecologic malignancy and IgG4-RD. In the cases presented, serial imaging with FDG PET/CT was used to identify and monitor temporal changes in metabolic activity in multiple tissue sites when the tissue diagnosis was still unclear. Ultimately,

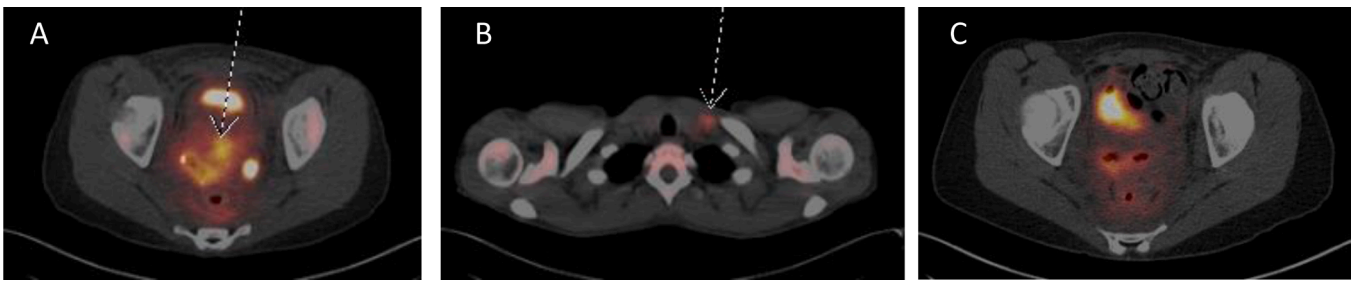

Fig. 2. Radiologic findings for case report 2, suspected recurrent cervical cancer. (A) Axial PET/CT FDG showing hypermetabolic activity of the endocervical cavity concerning for cancer recurrence. (B) Axial PET/CT FDG showing a hypermetabolic left supraclavicular lymph node. (C) Axial PET/CT FDG showing decreased metabolic activity in the pelvis after diagnosis and steroid treatment for IgG4-RD.

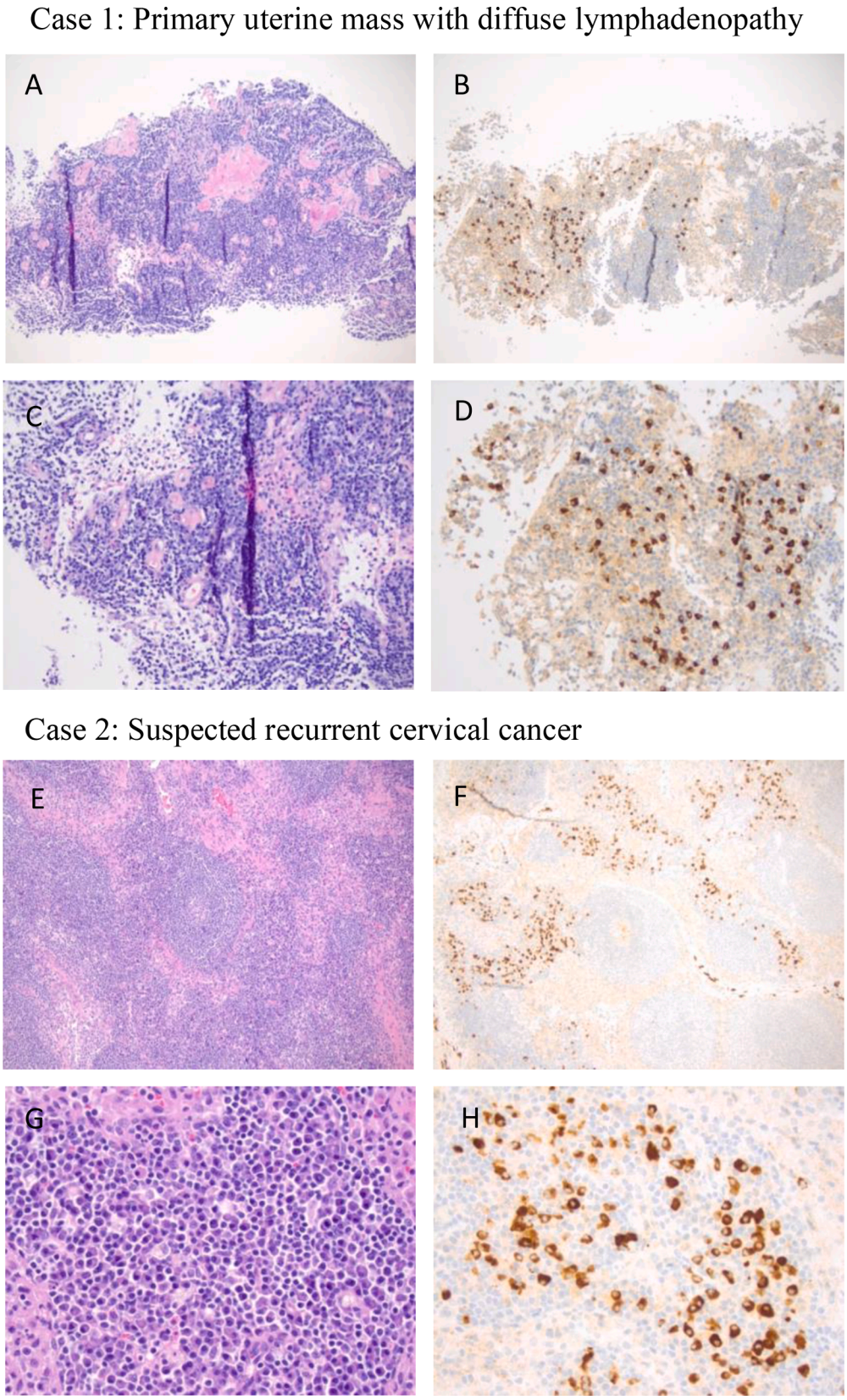

Fig. 3. Histologic findings demonstrating IgG4 + plasma cells from lymph node biopsies in case report #1 (uterine mass with diffuse lymphadenopathy) and case report #2 (suspected recurrent cervical cancer). (A, C) Hematoxylin and eosin (H&E) stain of excised left inguinal lymph node showing abundant plasma cells at 10× and 20× magnification, respectively. (B, D) Increased IgG4 expression in plasma cells at 10× and 20× magnification, respectively. (E, G) Hematoxylin and eosin (H&E) stain of excised left supraclavicular lymph node showing abundant plasma cells at 10× and 40× magnification, respectively. (F, H) Increased IgG4 expression in plasma cells at 10× and 40× magnification, respectively.

tissue biopsies confirming the underlying cause of the PET abnormalities were critical in these patients to avoid unnecessary and incorrect therapies. While tissue histopathology is the cornerstone of differentiating and diagnosing these distinct disease processes, previous literature demonstrates that FDG PET/CT is highly effective in determining extent of organ involvement and identifying sites for tissue biopsy in IgG4-RD (Tang et al., 2021). In both cases, the tissue biopsy sites that yielded positive IgG4 plasma cells confirming IgG4-RD diagnosis were determined based on PET imaging showing hypermetabolic lymph node activity. PET/CT can also be used to monitor response to treatment in IgG4-RD (Orozco-Gálvez et al., 2021), as was demonstrated in the second case. However, PET/CT has low specificity and normal/physiologic variants should be considered.

In conclusion, we report two cases in which IgG4-RD mimicked gynecologic malignancy. In cases in which suspicious gynecologic masses are accompanied by other systemic or non-specific symptoms (i.e., weight loss, anemia, joint pain, diffuse lymphadenopathy), serum studies of inflammatory markers and biopsies may be diagnostic and less morbid than mass excision or hysterectomy. IgG4-RD can coexist with gynecologic malignancy or mimic recurrence after initial treatment response. Imaging with PET may help determine extent of organ involvement, guide sites for tissue biopsy, and monitor response to treatment. Unusual patterns of lymphadenopathy should raise suspicion for non-malignant systemic diseases, including IgG4-RD, when considering the differential for patients with clinical manifestations concerning for advanced gynecologic malignancy and metastatic disease progression or recurrence.

CRediT authorship contribution statement

Rachel R. Pacyna: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Nicole A. Cipriani:** Resources, Writing – review & editing, Visualization. **Melvy S. Mathew:** Resources, Writing – review & editing, Visualization. **Josephine S. Kim:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

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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