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Case Report

A rare case of immune-related pseudotumor of ovary mimicking ovarian malignancy

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ABSTRACT

IgG4-related disease (IgG4-RD) is a chronic inflammatory condition affecting various body organs. However, genital tract involvement is rarely reported. A 40 years old reproductive-age woman presented with a solid abdominopelvic mass of 20 weeks size. CECT revealed a large multiloculated solid cystic lesion arising from right adnexa with multiple enlarged lymph nodes and omental thickening with gross right-sided hydroureteronephrosis suggestive of ovarian malignancy stage III. Surprisingly, tumor markers were normal. Intraoperatively, we noticed a 15×15 cm right ovarian mass encasing the right ureter all around and constricting it. The mass was densely adherent to recto-sigmoid and right pelvic wall, which mandated extensive surgery. Histopathological examination with immuno-histo-chemistry (IHC) suggested the diagnosis of IgG4-RD of ovary. Awareness about its occurrence in ovary will help in arriving at the diagnosis which may influence the extent of surgery. Lymphoplasmacytic infiltration with fibrosis in histopathological examination warrants IHC analysis for achieving a diagnosis.

Keywords: IgG4-RD, Immunoglobulin G4, IHC, Lymphoplasmacytic infiltration, Ovary

INTRODUCTION

IgG4-related disease (IgG4-RD) is a chronic inflammatory, relapsing-remitting condition characterized by the infiltration of tissues by lymphocytes and IgG4-secreting plasma cells resulting in various degrees of fibrosis. It can involve one or multiple sites in the body, either in a synchronous or metachronous fashion. Inflammation and deposition of connective tissue in the affected organs lead to organ dysfunction, organ failure, or even death if not treated.[1] A literature review shows that IgG4-RD affects the pancreas, bile duct, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidney, prostate, arteries, lymph nodes, skin, and breast.[2] Clinical symptoms vary depending on the organ affected. The disease produces organomegaly due to hypertrophy, obstructive symptoms, or organ dysfunction.[3] Though this condition can involve any site in the body, genital tract affection is reported rarely. Here, we report a case of IgG4-RD of the ovary, mimicking ovarian malignancy.

CASE REPORT

A 40 years old reproductive-age multiparous woman presented with complaints of pain and swelling in her lower abdomen for the past month. There was no fever, menstrual disturbance, or urinary disturbance in the recent past. She did not experience loss of appetite or loss of weight. Apart from having hypertension, she did not suffer from any other medical illness or undergo any surgery in the past. She had been using a Copper containing intrauterine device for contraception. There was no history of any significant illness or malignancy in her family. Her vitals, general physical examination, and other systemic examinations were normal. On abdominopelvic examination, there was a midline mass of 20 weeks' size arising from the pelvis, extending up to the umbilicus,

which was irregular in shape, firm in consistency, non-tender, and restricted mobility. There was no free fluid in the abdomen. There was no tenderness on cervical movement or nodularity in the pouch of Douglas. Rectal mucosa was smooth.

Investigations

Her routine blood investigations were normal. Ultrasound revealed a multiloculated, multiseptated cystic lesion of size 11.3×10.4×10.7 cm in the right adnexa. The right ovary is not visualized separately. The uterus appeared normal. There was no free fluid. Right-sided hydroureteronephrosis was present. Ultrasound features suggested mucinous cystadenocarcinoma in the right ovary. Tumor markers (beta HCG<0.05, CA125-13.3 u /mL, CA 19.9-22 U/mL, CEA-1.04 ng /mL, LDH-225 IU /L) were reported as normal. Fine needle aspiration cytology (FNAC) from the mass was inconclusive. Contrast-enhanced computed tomography (CECT) revealed a well-defined heterogenous multiloculated solid-cystic lesion with a predominant cystic component of size 9.8×13.6×12.8 cm noted arising from the right adnexa and extending to the left side with internal septations of thickness ranging from 4 mm to 2 cm (Figure 1 A and B). Ovaries were not identified separately. Multiple, enlarged, enhancing lymph nodes were seen in the pelvic, pre-aortic, and para-aortic regions up to the infrarenal plane (Figure 2). Omentum showed a few sub-centimetric enhancing deposits. There was no free fluid in the pelvis and no evidence of metastasis in the abdomen and thorax. There was no mediastinal lymph node enlargement in thorax CT. According to CE CT, the impression was stage III (FIGO) malignant ovarian tumor with involvement of omentum and retroperitoneal lymph nodes.

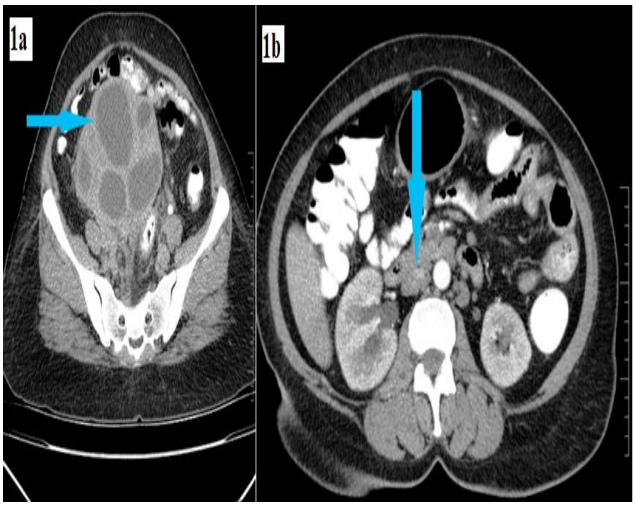

Figure 1: (a) CECT axial image. Shows a well-defined heterogenous multiloculated pelvic solid cystic lesion with a predominant cystic component; (b) CECT axial image showing multiple enlarged enhancing lymph nodes (marked by bold arrow) in pre-aortic and para-aortic regions with right-sided hydroureteronephrosis.

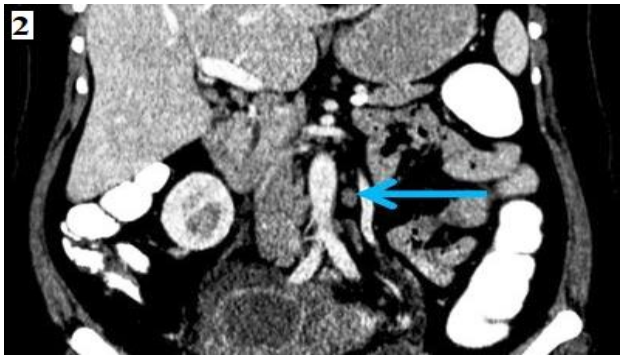

Figure 2: CECT coronal image with arrow mark showing para-aortic lymph nodal enlargement till infrarenal area.

Treatment

The patient was taken up for primary cytoreductive surgery. Intraoperatively, there was a right ovarian mass of 15×15 cm (Figure 3 A and B) with infiltration into sigmoid and upper rectum, also encasing right lower ureter and constricting it, and mass was densely adherent to right-Iliac vessels. Multiple large pelvic and para-aortic lymph nodes of size 2×1 cm were present. Omentum, peritoneum and small bowel appeared normal. There was a loss of surgical plane between tumor and rectum due to extensive fibrosis. Hence it was decided to do resection of rectum to give complete clearance of disease. Total abdominal hysterectomy with bilateral salphingo-oophorectomy with low anterior resection of the rectum, resection of the lower part of the right ureter with reimplantation, and double-J stenting, along with bilateral pelvic and para-aortic lymphadenectomy, infra-colic omentectomy, and sigmoid end colostomy was done. Extensive surgery was done with the intention to provide optimal debulking in view of the preoperative diagnosis of stage III ovarian malignancy. As our preoperative diagnosis was stage III ovarian cancer, we did not perform a frozen section during surgery. Complete resection of tumor was done without the residual disease.

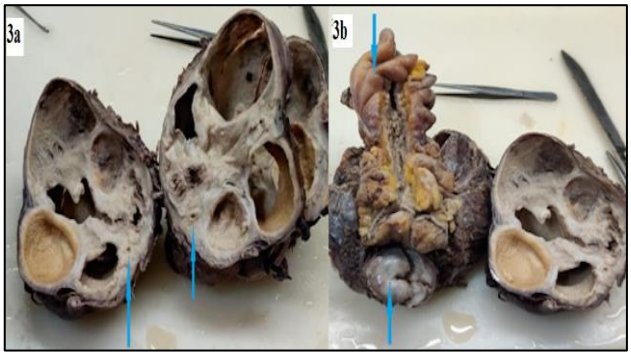

Figure 3: (a) A cut section of a right ovarian mass. Thickness of solid area ranges from 4-2 cm. No papillary excrescences were noted, up facing arrow showing ureter encasement into the tumor; (b) inferior view of specimen, up-facing arrow shows cervix. A down-facing arrow shows a rectosigmoid.

Histopathological examination (HPE) showed fibro-collagenous tissue with extensive infiltration by dense chronic inflammatory cells composed of plasma cells and lymphocytes, admixed at places with foamy histiocytes, eosinophils and Russel bodies (Figure 4 A and B). There was no evidence of malignancy. Resected sigmoid colon showed infiltration of the entire bowel wall from serosa to lamina propria with lymphocytes and plasma cells. Proximal and distal resected colon margins were free of infiltrates. The entire segment of the resected ureter was found to be infiltrated with inflammatory cells. Lymph nodes showed follicular hyperplasia. Omentum showed a few lymph nodes with reactive hyperplasia. Repeat HPE with IHC markers (Figure 5 A and B) revealed an IgG4: IgG ratio of 70% favoring the diagnosis of IgG4-RD.

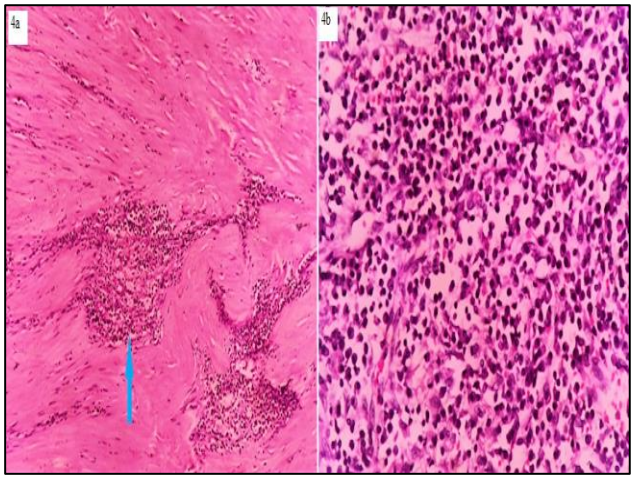

Figure 4: (a) Histopathological section from ovary showing extensive fibrosis (arrow) with infiltration by plasma cells, lymphocytes, and histiocytes (H and E, 10X); (b) infiltration by predominantly plasma cells and few lymphocytes (H and E, 40X).

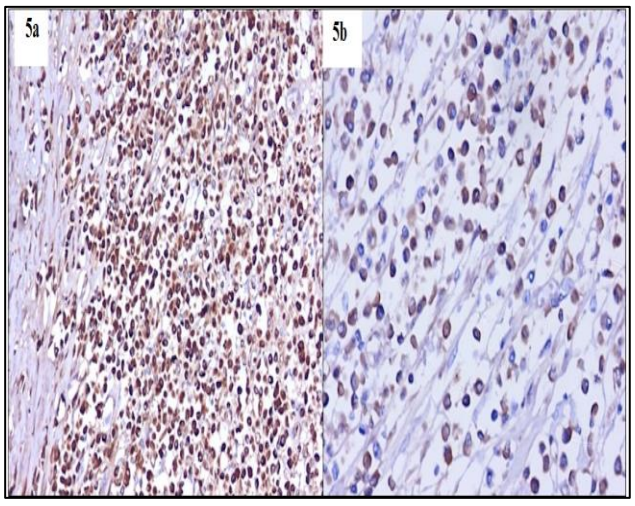

Figure 5: (a) IHC staining for IgG and IHC staining for IgG4; (b) a comparison of both images shows the IgG4 to IgG ratio of more than 70%.

Outcome and follow-up

Whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) done two months after surgery did not reveal any evidence of metabolically active disease and IgG4 level was 3.19 mg/dl. Six months after primary surgery, colostomy reversal and Colo-rectal anastomosis were done, and the patient recovered well. Her IgG4 levels in the 6-month follow-up were normal. She was advised for further follow-up with a PET-CT scan and repeat IgG4 levels after six months, and then annually.

DISCUSSION

Only 5 cases of IgG4-RD in the ovary have been reported so far.[4-8] Literature reveals two case reports with uterine affection.[9,10] Diagnosis of IgG4-RD was arrived upon postoperatively in all these cases. Four out of 5 ovarian IgG4-RD cases were diagnosed preoperatively as ovarian neoplasm. All these cases showed lymphoplasmacytic infiltration with fibrosis on histopathological examination. IHC confirmed the diagnosis post-surgery.

Comprehensive clinical diagnostic criteria (CCD) include three standards for diagnosing IgG4-RD.[3] They are organomegaly, elevated serum IgG4 concentrations (> 135 mg/dl), and histopathological examination (HPE) showing marked lymphocyte and plasma cell infiltration, storiform fibrosis, and IgG4/IgG ratio of > 40% by IHC.

The etiology of IgG4-RD is still not clearly understood. Research reveals autoimmunity and infectious agents to be potential immunologic triggers. Immune-mediated reaction with predominant type 2 helper T cell activity causes over-expression of interleukins and transforming growth factor β.[11] These cytokines contribute to an elevation in eosinophils, IgG4, and IgE concentrations, with progressive fibrosis which is characteristic of IgG4 RD. Massive infiltration by inflammatory cells results in tumefactive enlargement of the affected sites and organ dysfunction.

Though literature quotes many intraperitoneal organ affections with IgG4-RD, reproductive organ affection is rare. Because of the rarity of the diagnosis in the reproductive organ, we had difficulty arriving at the diagnosis preoperatively and during the histopathological examination.

Solid and fixed abdominopelvic mass with multiple locules, thick septations, omental thickening, and enlarged lymph nodes in CECT, supported the diagnosis of ovarian malignancy in our case. However, the absence of ascites with such a large mass remained an exception to the usual clinical scenario of ovarian malignancy. Usually, in abdominal tuberculosis, there is fat stranding in the omental and peritoneal lesions and shows peripherally enhancing necrotic nodes. Tuberculosis was not considered in the initial workup since there was no history

of evening rise of temperature, loss of weight and appetite, and absence of ascites and pleural effusion. Though HPE revealed an initial diagnosis of ovarian abscess, re-evaluation helped us arrive at the diagnosis. Histopathological examination of enlarged lymph nodes in our case showed follicular hyperplasia, a reactive enlargement due to IgG4-RD.

Advanced ovarian malignancy with extensive lymph nodal involvement is usually associated with ascites. In the setting of a complex ovarian mass with multiple lymph node enlargements in the absence of ascites and abnormal tumor marker levels, we should also consider non-neoplastic causes in the differential diagnosis. No stringent radiological diagnostic criteria are defined in the literature for IgG4-RD of the ovary. Though FNAC was done preoperatively in our case, lack of awareness about its occurrence in the ovary may be a reason for not arriving at the diagnosis. In such a situation, a repeat biopsy preoperatively or frozen section intraoperatively would help in arriving at the diagnosis.

With only a handful of cases reported in reproductive organs, no consensus has been derived so far as a standard of care. 2015 consensus statement on the management and treatment of IgG4-RD strongly suggests glucocorticoids as the standard first-line treatment for active disease.[1] Maintenance steroids are usually given following the achievement of remission with medical therapy. There is a general agreement that patients who were at elevated risk of relapse are likely to benefit from maintenance therapy.[1] Those with a multiorgan disease, significantly elevated serum IgG4 levels, organ-threatening IgG4-RD manifestations, and a previous history of relapse are considered high-risk groups for future relapse.

Contradictory to the above evidence, relapses have been reported in spite of steroid maintenance therapy.[12,13] 2015 consensus statement mentions that some long-standing highly fibrotic lesions may poorly respond to pharmacological agents.[1] Based on the anatomical location of the lesion and involvement of adjacent structures, surgical resection may be considered an option.

Usually, surgically resected IgG4-RD of the gastrointestinal tract remains as a postoperative diagnosis, where surgery is being done for suspected malignancy.[14,15] Literature shows successful treatment of IgG4-RD of the mesentery, lungs, and orbital lesions with surgery, without the need for maintenance steroids.[16-19] Follow-up of these cases for variable periods of time did not show any relapse. All the cases with IgG4-RD of the ovary reported so far in the literature were surgically resected and were incidentally detected postoperatively.[4-8] None of them reported relapse of disease or requirement of maintenance therapy in their cases. To date, 24 months following surgery, our case did not show any relapse.

Considering the facts that 1) most of the IgG4-RD relapses respond well to glucocorticoid therapy, 2) the possibility of side effects with even low dose of glucocorticoids, 3) documented complete surgical clearance of disease in our patient with normal IgG4 levels and no active disease in PET-CT, and 4) assured follow-up of the patient, we decided to wait and watch, without starting on maintenance steroid therapy.

To conclude, for diseases involving multiple systems or vital structures, medical management with steroids remain the first line of management. It is crucial to diagnose early and start treatment immediately, as delaying the diagnosis can lead to fatal fibrosis. If an IgG4-RD is causing a localized huge mass in structures where complete resection is possible, surgical clearance can also be considered an option. Long-term follow-up of all surgically resected cases in literature will provide a piece of foolproof evidence for reaching a consensus. Postoperatively, the patients should be followed up with PET-CT for residual lesions. As there are reports of malignancies occurring in patients with IgG4-RD, it is mandatory to have a close follow-up of the patients by the specialist.

CONCLUSION

In the case of solid or multiloculated cystic ovarian mass with multiple lymph node enlargements, without ascites and normal levels of tumor markers, IgG4-RD should be considered as one of the differential diagnoses. Dense adhesions may be present in IgG4-RD due to inflammation and fibrosis, requiring extensive surgery. Lymphoplasmacytic infiltration with fibrosis in histopathological examination warrants IHC analysis for achieving the diagnosis. Awareness about its occurrence in the ovary and performing preoperative FNAC will help in arriving at the diagnosis. If preoperative FNAC does not give a conclusive diagnosis, a biopsy has to be done to arrive at a definitive diagnosis. A frozen section of the specimen should be performed in all doubtful cases.

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