Case Report

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Unusual Presentation of Intractable Ascites and Pleural Effusion as a Sole Manifestation of IgG4 Related Disease: A Case Report

Roy Hershenson*, Eli Karniel, Eyal Robinson, Lidiya Maor, Leonid Galin, Irit Kaye, Anna Shoykhet, Muhamad Agbaria, Ekaterina Muzykovskaia and Gideon Charach

Department of Internal Medicine B, Meir Medical Center, Kfar Saba, Israel

***Corresponding author:** Roy Hershenson, Department of Internal Medicine B, Meir Medical Center, Kfar Saba, Israel

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ABSTRACT

Keywords: IgG4-Related Disease; Polyserous Effusions

Abbreviations: HPF: High Power Field; TB: Tuberculosis; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; PCR: Polymerase Chain Reaction; CT: Computed Tomography; FDG: Fluorodeoxyglucose; PET-CT: Positron-Emission Tomography

Introduction

IgG4-related disease (IgG4-RD) is a rare immune-mediated condition associated with fibro-inflammatory lesions. It was first recognized as a distinct disease in 2003 [1,2]. It is a disease of middle-aged patients, with a mean age at diagnosis of approximately 60 years old that predominates in men [1]. It often presents as a multi-organ disease occurring in a synchronous or metachronous fashion with a tendency to form tumor-like lesions in almost every organ or system [1]. It may be misdiagnosed as malignancy, infection or other immune-mediated conditions, and can lead to organ dysfunction, organ failure and death [2]. Although IgG4-RD can affect almost any organ, there is a strong predilection to certain organs, including the pancreas, the biliary tree, the major salivary and lacrimal glands, the aorta and retroperitoneum [1,2]. Serosal involvement is uncommon and has been rarely reported [3]. IgG4-RD is diagnosed based on a combination of clinical, serological, radiological and pathological findings. The pathological characteristic features of the disease include a diffuse lymphoplasmacytic infiltration with abundant IgG4 positive plasma cells, obliterative phlebitis and storiform fibrosis [1,2]. The presence of more than 10 IgG4-positive plasma cells per High power field (HPF) and an IgG4/IgG positive plasma cell ratio of more than 40% is also important. Most patients show elevated serum IgG4 levels; however, 30% to 50% have normal serum IgG4 concentrations despite classic histopathological and immunohistochemical findings [1]. We describe a case of a patient with IgG4-RD, manifested solely as retractable ascites and pleural effusion.

Case Report

A 52-year-old female patient of Arab ethnicity was admitted to our department due to worsening exertional dyspnea and ambulatory findings of right sided pleural effusion and ascites. Her past medical history consisted of diabetes type II, essential hypertension and dyslipidemia. On admission, she complained of dyspnea and increased abdominal girth. She denied fever, night sweats or weight loss, as well as any other respiratory, cardiovascular, neurologic, gastrointestinal, or genitourinary symptoms. She had no history of exposure to tuberculosis (TB). Physical examination revealed findings of right-sided pleural effusion and ascites. The remainder of her physical examination was normal. Laboratory findings showed anemia of chronic disease with normal white blood cell and platelet counts. Kidney and liver function tests were normal and albumin level was 3 g/dL. She had elevated inflammatory markers, with a C-reactive protein (CRP)

level 4 mg/dL and erythrocyte sedimentation rate (ESR) of 120. Various virologic and autoimmune serologic analyses were normal, including ANA, anti-dsDNA, anti-Smith, C3, C4, RF and ANCA. Serum IgG4 level was slightly elevated at 95.5 mg/dL (upper limit of normal: 86.4).

Chest X-ray revealed pleural effusion on the right side, with no evidence of consolidation or pulmonary edema. Pleuro-centesis demonstrated an exudative infiltrate. Peritoneal centesis showed inflammatory ascites with a low serum-ascites albumin gradient of 0.2 g/dL, 1200 WBC, of which 99% were lymphocytes. Cytology from pleural and ascetic fluids showed no atypical or malignant cells. Bacterial cultures of peritoneal and pleural fluid were negative and acid-fast stain and polymerase chain reaction (PCR) for TB were also negative. Flow cytometry from ascetic fluid showed 98% CD3 cells, mixed population of CD4 and CD8 cells, with no signs of monoclonality. PCR for pan-bacteria, pan-mycobacteria and pan-fungal was negative. A 24-hour urine collection was negative for proteinuria. Stool alpha-1 antitrypsin level was normal. Trans-thoracic echocardiography showed bilateral pleural effusions, with normal LV wall motion and no signs of pericardial effusion. Abdominal ultrasound was normal, including normal flow of hepatic veins and arteries on Doppler. Vaginal ultrasound showed pelvic fluid without evidence of malignancy.

Computed tomography (CT) scan of the chest, abdomen and pelvis, with intravenous contrast, showed pleural effusions and ascites with no evidence of any other pathology. 18F-fluorodeoxyglucose (FDG)-positron-emission tomography (PET-CT) scan demonstrated right pleural effusion with no FDG intake in the chest and a large ascites with a high FDG intake. It further showed thickening of the peritoneum with congestion in the mesenterial fat and an infiltration of the mesenterial fat on the right. Endoscopic investigation was normal. The patient underwent a bone marrow aspiration and biopsy which showed no signs of infection or malignancy. During the investigation, the patient was admitted several times to our department due to worsening dyspnea and early satiety, with recurrent pleural effusions and ascites that required therapeutic centesis once every two weeks. Her albumin level continued to decline and deteriorated to 1.7 g/dL. The patient was treated with intravenous albumin replacement therapy. We decided to proceed with explorative laparoscopy, which showed normal macroscopic appearance of the peritoneum and mesenterial fat. Part of the omentum that was attached to the uterus was removed. As part of diagnosis or exclusion of Meigs syndrome, the patient underwent a bilateral salpingo-oophorectomy.

Pathology showed normal ovaries. The omentum showed patches of fibrosis along with lymphoplasmacytic infiltration within the omentum and around blood vessels, without the classic appearance of storiform fibrosis or obliterative phlebitis. There were numerous plasma cells, including 40 IgG4 positive plasma cells per HPF (Figure 1). Plasmablast level in the peripheral blood was 1,165/ml. At that point, probable IgG4-RD with chronic inflammatory serositis was diagnosed and treatment with high dose steroids was commenced, with IV methylprednisolone for 3 days, followed with 60 mg per day prednisone. The patient improved quickly, with a diminished frequency of repeated centesis. Her albumin level increased to 3.6 g/dL and CRP declined to 0. An attempt to reduce the dose of prednisone more quickly due to uncontrolled hyperglycemia led to rapid reaccumulation of ascites and pleural effusion. Slow tapering of prednisone dose over the course of two months was successful, with no need for centesis and a stable albumin level.

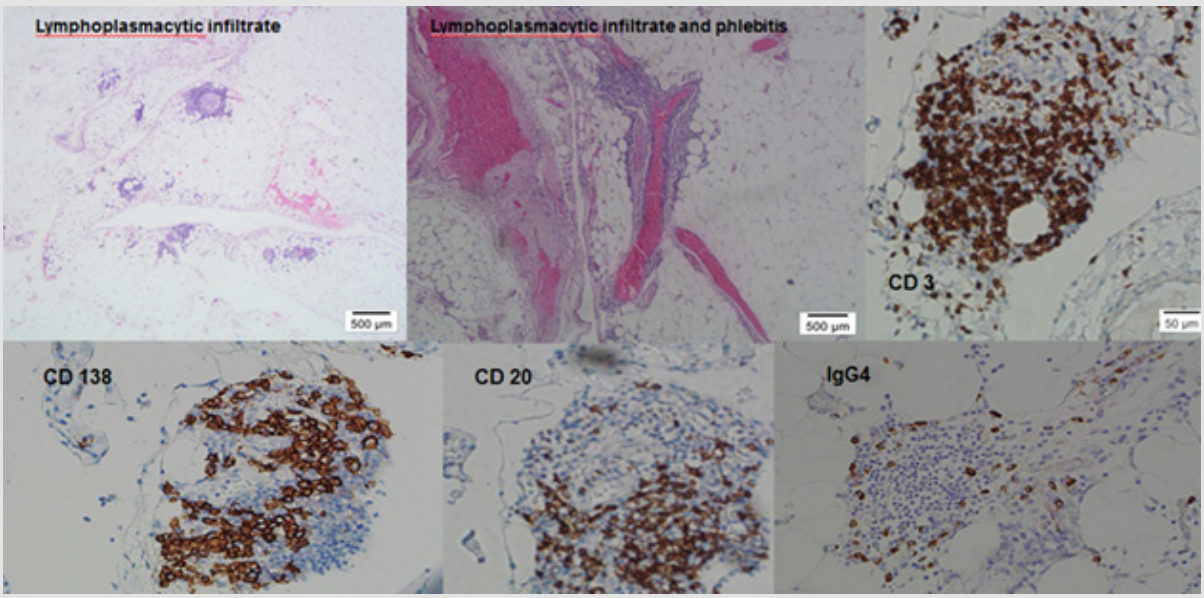

Figure 1.

Discussion

Here, we reported a unique case of a woman who was admitted to our department due to recurrent pleural effusion and ascites, that was finally found to be probable IgG4-RD with chronic inflammatory serositis, according to the histopathologic and immunohistochemical examination. Given the multi-organ nature of IgG4-RD, and the absence of a single diagnostic feature, classification criteria for IgG4-RD were developed by the American College of Rheumatology and the European League against Rheumatism. These criteria are composed of a three-step process including:

1. Fulfillment of the entry criteria (characteristic clinical, radiological or pathological features);

2. Exclusion criteria that consist of various clinical, serological, radiological and pathological findings; and

3. Inclusion criteria that address clinical, serological, radiological and pathological findings that are each weighted differently. A threshold of 20 points was set, to arrive to a confident decision that a patient should be classified as having an IgG-RD, with 82% sensitivity and specificity of 97.8% [2]. Our patient met the entry criteria and the exclusion criteria. Although she only partially met the inclusion criteria - not sufficient to pass the threshold of 20 points. Nevertheless, it should be emphasized that the purpose of the classification criteria is to facilitate the identification and inclusion of homogenous groups of patients into clinical trials, and they are not intended to be used to establish a diagnosis of IgG4-RD in clinical practice, nor to guide the management of patients with suspected IgG4-RD, accordingly [2]. With the growing recognition of the wide spectrum of manifestations of IgG4-RD, these classification criteria cannot include all patients within the spectrum of the disease.

The present case has several distinctive features. First, the patient presented with a sole manifestation of recurrent peritoneal and pleural effusions, with the primary inflammatory focus in the peritoneum, as indicated by the PET-CT. There was neither a classic tumor-like lesion nor any other organ involvement. Serosal involvement as a manifestation of IgG4-RD has been reported infrequently in the literature and in the majority of these cases, was not the only manifestation of the disease [3]. Peritoneal involvement has been rarely reported as a manifestation of IgG4-RD, and pleural effusions are thought to be unusual and seldom dominate the clinical picture. The most frequently involved sites reported in association with IgG4-related pleural disease are the lungs, pericardium, mediastinum and pancreas [3]. It is now believed that serosal involvement in IgG4-RD is more frequent than previously thought and that therefore, IgG4-RD should be considered in the differential diagnosis of serositis and should be ruled out as a possible underlying cause.

Second, even-though the pathological findings were consistent with IgG4-RD, including fibrosis, lymphoplasmacytic infiltration and 40 IgG4 positive plasma cells per HPF, the characteristic findings of obliterative phlebitis and storiform fibrosis were absent. With the growing recognition of IgG4-RD, it is now diagnosed using increasingly small biopsy samples that frequently do not demonstrate the full spectrum of pathological findings [2]. Third, the patient's serum IgG4 levels were only mildly increased. Serum IgG4 levels are normal in a substantial percentage of patients with IgG4-RD, depending on the organs involved and on the severity of the disease [1]. Elevated serum IgG4 level is no longer considered essential to the diagnosis [2]. Lastly, the patient in this case had an elevated plasmablast level, and this finding contributed to the diagnosis. Patients with IgG4-RD express an increased level of plasmablasts [4]. The peripheral plasmablast level is positively correlated with serum IgG4 levels, the number of organs involved and ESR and decreases after treatment [4,5]. It has also been found that the median plasmablast count was not significantly lower in IgG4-RD patients, with normal serum IgG4 concentrations, compared to those with elevated serum IgG4[5]. Therefore, plasmablasts might be a potentially useful biomarker for the diagnosis of IgG4-RD and for assessing response to treatment and appear to be a superior biomarker to serum IgG4 concentrations [5].

Conclusion

IgG4-RD can manifest with serositis and serosal effusions, which can be the sole manifestation of the disease. IgG4 related effusions are an under-diagnosed condition. Given the fact that IgG4-RD can be effectively treated, it is imperative to properly investigate serosal effusions for IgG4-RD.

Author Contribution

RH,GC, EK - Treatment of the patient, conception, interpretation of data and drafting of the manuscript.

GC, LM, MA – Treatment of the patient, major revision and final approval of the manuscript.

ER, AS, IK, LG, EM, – revision of the manuscript and treatment of the patient

Department of Internal Medicine B, Meir Medical Center, Kfar Saba, Israel, affiliated with Sackler Medical School, Tel Aviv University, Tel Aviv, Israel.

Conflict of Interest

None to declare.

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