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CASE REPORT

Waldenström's macroglobulinemia masquerading as ovarian cancer with peritoneal carcinomatosis, ascites, and elevated CA-125

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Abstract
Waldenström's macroglobulinemia is a rare hematology malignancy which often presents with ''B symptoms,'' anemia, and thrombocytopenia. A 46-year-old woman presented with 2 months of abdominal distension accompanied by an unintentional 20-lb weight loss. Her abdominal CT scan demonstrated diffuse carcinomatosis with bilateral ovarian lesions and screening labs revealed a markedly elevated CA-125, suggesting a diagnosis of ovarian cancer. Upon admission for workup, patient was found to have a significant protein gap, later attributed to a markedly elevated IgM. Omental and bone marrow biopsy confirmed the diagnosis of Waldenström's macroglobulinemia, with elevation in CA-125 thought to be secondary to peritoneal irritation. This patient has since been successfully treated with six cycles of bendamusine and rituximab with no evidence of disease on staging scans and normalization of both CA-125 and IgM. To our knowledge, this is the first documented case of Waldenström's macroglobulinemia presenting with symptoms classically associated with ovarian cancer and demonstrates the importance of maintaining a broad differential when evaluating patients with abdominal carcinomatosis.

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Introduction

Waldenström's macroglobulinemia (WM) is a relatively rare disease with an incidence of 3 cases per million people per year, accounting for 1—2% of hematologic malignancies [1]. Clinical sequelae are typically driven by an overabundance of large 970-kDa serum immunoglobulin M (IgM) monoclonal proteins and by infiltration of hematologic tissues with lymphoplasmacytic lymphoma (LPL). The most common presenting symptoms at diagnosis include anemia, hyperviscosity, ''B symptoms,'' bleeding, and neurological symptoms [2]. We describe an unusual presentation of WM in a 46-year-old lady with abdominal pain, constipation, markedly elevated cancer antigen 125 (CA-125), fatigue, weight loss, and evidence of peritoneal carcinomatosis on abdominal/pelvic computed tomography (CT) scan. The patient was initially thought to have advanced ovarian carcinoma.

CA-125 is a glycoprotein antigen historically associated with ovarian cancer, and its clinical utility as a biochemical tumor marker for cancer screening has been widely studied. To date, CA-125 is the most utilized and sensitive marker in the management of ovarian cancer at various stages of the disease [3]. Ovarian cancer is the seventh most common cancer in women and has an incidence rate of 120.5 cases per million [4]. Advanced ovarian carcinoma commonly presents with abdominal distension, abdominal pain, fatigue, bloating, and constipation, largely secondary to the presence of ascites and peritoneal metastases [5,6]. The workup of our patient with symptoms concerning for ovarian carcinoma resulted in a diagnosis of WM. To our knowledge, this is the first case report of WM presenting with abdominal carcinomatosis and markedly elevated CA-125.

Case report

Our patient was an otherwise healthy 46-year-old woman who initially presented to her primary care physician with a 2-month history of constipation. She had noted abdominal distension that started approximately 1 month prior to presentation, dyspnea, unintentional 20-lb weight loss, and occasional nondrenching sweats. The patient had not seen a gynecologist or received a pap smear in more than 7 years. She has a 30-pack-a-year smoking history and 3—4 alcoholic drinks per night, but denied recent or past recreational drug use. Her family history was significant for breast cancer diagnosed at age 50 in her maternal aunt, and acute lymphocytic leukemia in her daughter and maternal aunt.

On examination, our patient appeared well nourished and in no acute distress. Her lungs were clear to auscultation with decreased inspiratory effort secondary to abdominal distension and cardiac exam was normal. Her abdomen was markedly distended with diffuse tenderness to palpation in all 4 quadrants with clinical evidence of moderate ascites yet with no palpable abdominal masses. She had no cervical, supraclavicular, axillary, or inguinal lymphadenopathy. She had 1+ pitting edema of lower extremities bilaterally.

On imaging, a CT of her abdomen demonstrated diffuse abdominal carcinomatosis with bilateral low-attenuation ovarian lesions measuring 1.6 cm $\times$ 1.1 cm with extensive ascites (Fig. 1). The patient was admitted to the James Comprehensive Cancer Center for further workup for presumed metastatic ovarian cancer.

The admission complete blood count revealed the following: white blood cell count, 7.1 K/μL (4.5—11.0 K/μL); hemoglobin, 12.3 g/dL (11.7—15.5) g/dL; mean corpuscular volume, 103.9 fL (81.0—100.0 fL); mean cell hemoglobin, 33.1 g/dL (27.0—34.0 g/dL), red blood cell distribution, 13.8 (32—36); platelet, 228 K/μL (150—400 K/μL); and mean platelet volume, 10.9 fL (7.5—11.2 fL). Additional laboratory results revealed grossly normal chemistry and an elevated CA-125 of 1057 U/mL (0—30 U/mL), further suggesting a primary ovarian neoplasm. She also had an increased total protein of 8.8 g/dL (6.4—8.3) with an albumin of 3.6 g/dL (3.7—4.9). Given the protein gap of 5.2 g/dL, serum protein electrophoresis and urine protein electrophoresis were ordered. The patient underwent ultrasound-guided omental biopsy and paracentesis. While waiting for the results of her omental biopsy, she was found to have monoclonal gammopathy with an M-protein level of 2883.5 mg/dL and a markedly elevated IgM level of 4463 mg/dL (45—281 mg/dL). Cytological examination of peritoneal fluid showed abundant atypical plasmacytoid cells, which were positive for CD138 and CD20 (Fig. 2A). The omental biopsy showed diffuse infiltration by lambda-restricted, strongly CD20+ small- to medium-sized

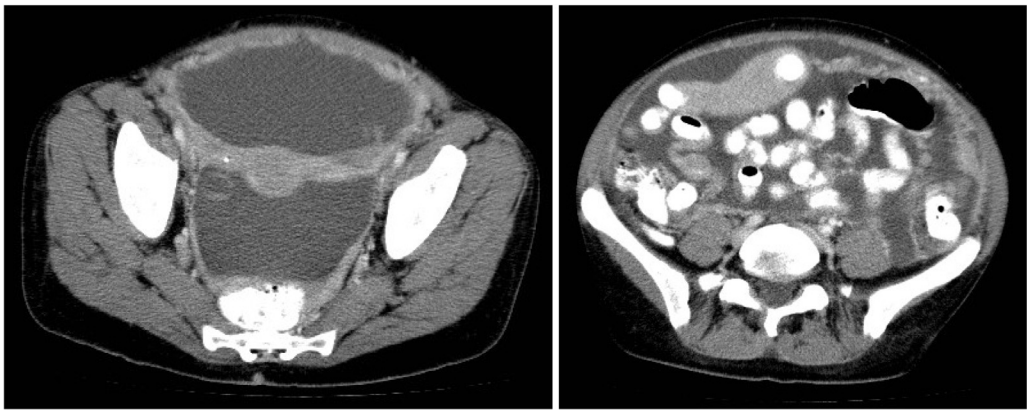

Fig. 1 Abdominal CT scan: revealing diffuse abdominal ascites, and bilateral ovarian lesions.

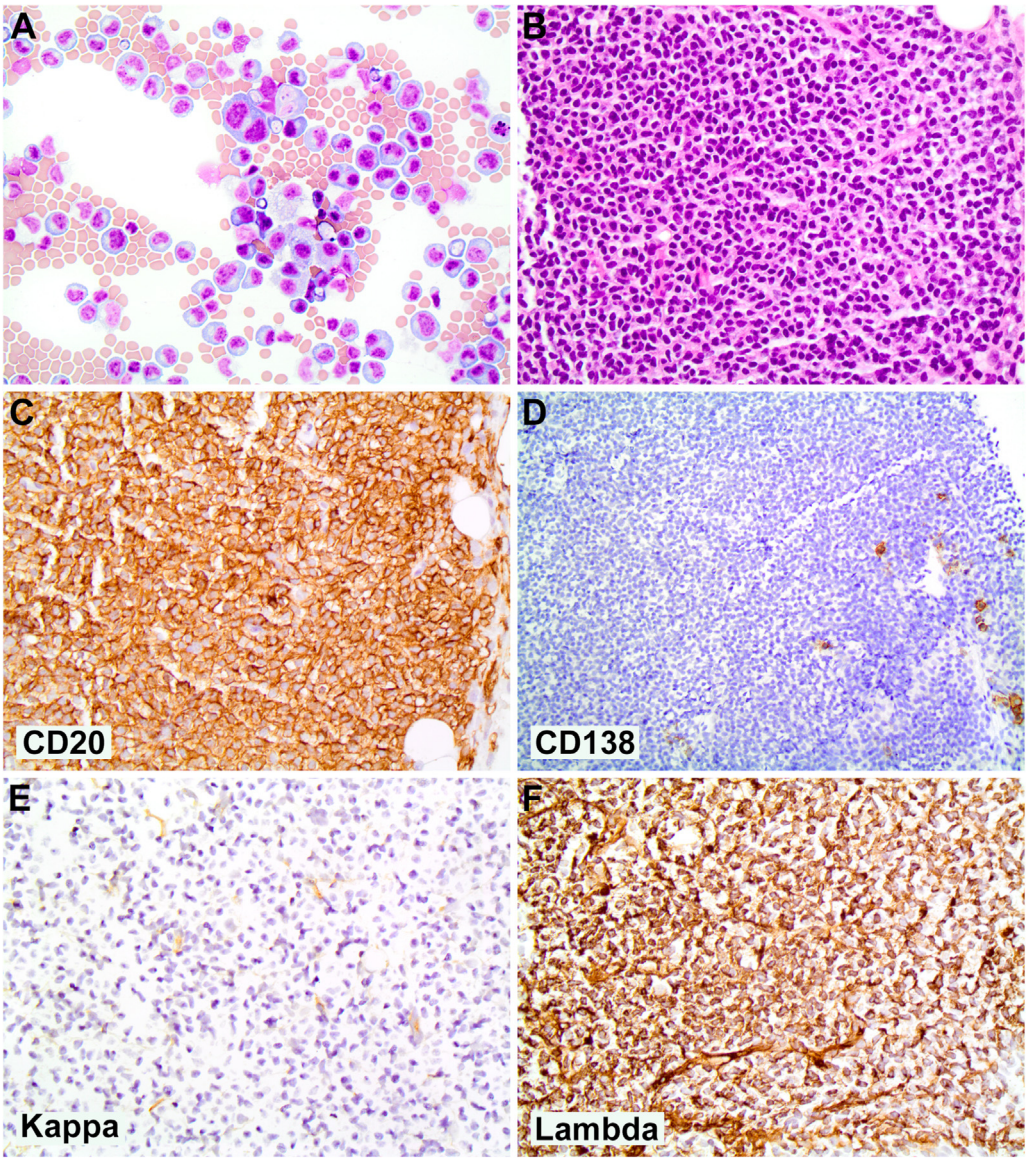

Fig. 2 Pathology analysis of diagnostic peritoneal biopsy and paracentesis: A: Peritoneal fluid cytology showing abundant atypical plasma cells, B: Omentum biopsy (H&E, 400×) Diffuse lymphoid infiltrate comprised of small to medium-sized, mature cells with occasional cells with plasmacytic appearance, C—E: IHC stains showing infiltrate is composed of CD20+, CD138- lambda-restricted B-lymphocytes.

lymphocytes with mature chromatin and absent nucleoli. A subset of lymphoid cells showed plasmacytoid differentiation with only rare mature plasma cells seen (Fig. 2B—F). B cells were negative for CD5—, CD10—, CD43—, bcl-1, and bcl-6, with only rare B cells showing a detectable expression of CD138 antigen. Omental biopsy was stained with Congo red and was negative for amyloid deposits.

Bone marrow aspiration and biopsy was subsequently performed and revealed 30—40% involvement by the same lambda-restricted B cells (Fig. 3). Flow cytometry on bone marrow demonstrated lambda-restricted B cells that expressed CD19 and CD20 with a small population coexpressing CD38 and CD138 antigens. Infiltration of the omentum and the bone marrow with low-grade lambda-restricted, CD20+, CD138—, IgM+ (cytoplasmic) B cells with markedly elevated serum IgM level confirmed the diagnosis of LPL with WM. The initial serum viscosity was 3.7 centipoises (cP) (normal reference 1.6—1.9 cP), yet the patient had no symptoms or signs of hyperviscosity syndrome-hence, plasma exchange was not indicated at presentation.

The patient was started on bendamustine (90 mg/m^2) for 2 days for rapid disease control without rituximab because of the marked elevation of serum viscosity and risk of hyperviscosity syndrome. She tolerated initiation of chemotherapy well and was discharged to follow-up for continued therapy. Further treatments were continued on outpatient basis, and rituximab (375 mg/m^2) was introduced on Day 1 in cycle 2; the patient completed a total of six cycles. After three cycles, her IgM was 247 mg/dL, her CA-125 was 6 U/L, and her serum viscosity was 1.7 cP. Repeat CT scan

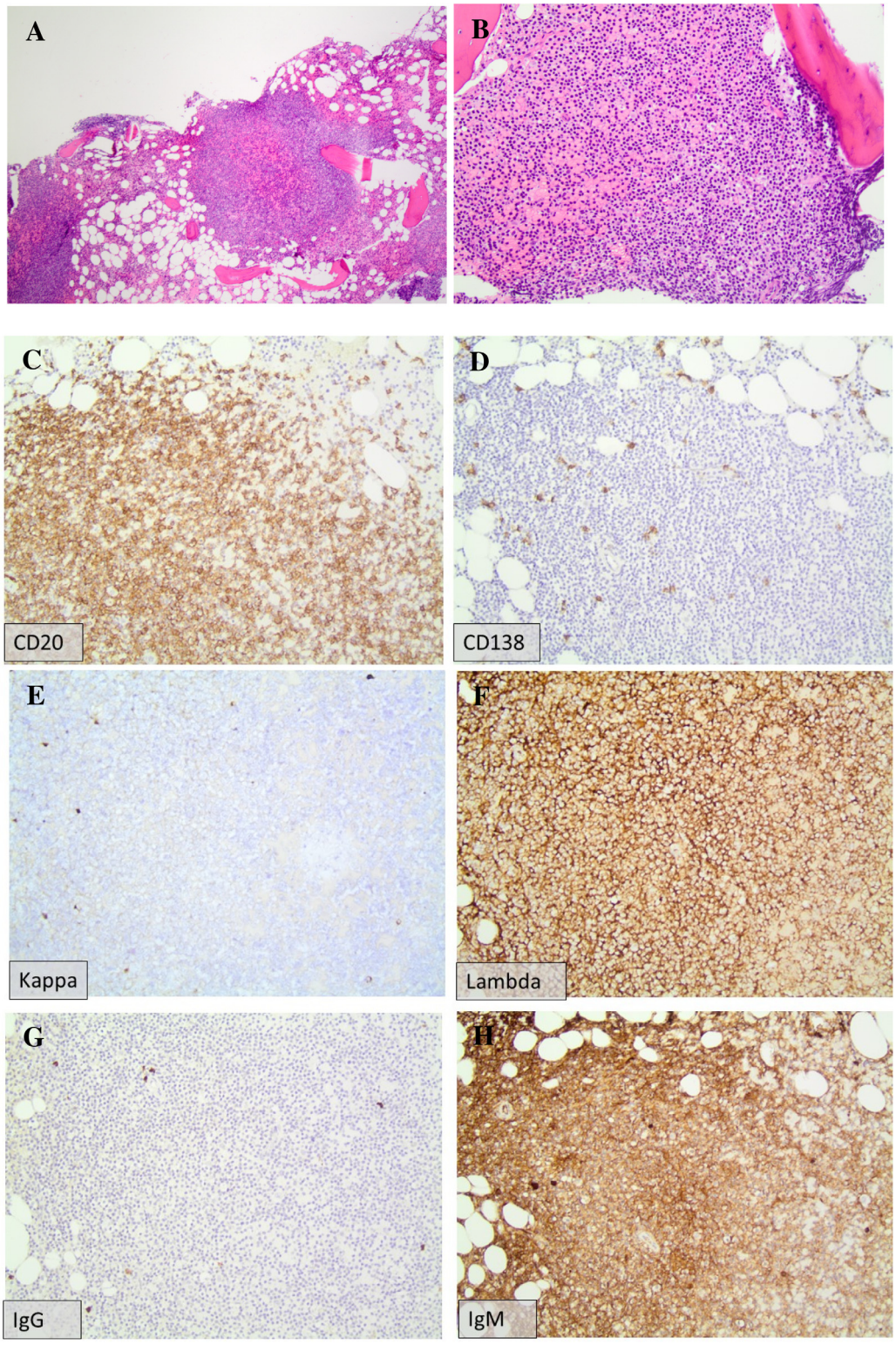

Fig. 3 Initial bone marrow biopsy; A (H&E 40×) and B (H&E 200×): atypical nodular lymphoid infiltrate comprised predominantly of small, mature cells with occasional forms with plasmacytic appearance, C—H: IHC stains showing infiltrate is composed of CD20+, CD138—, IgM+, lambda-restricted B-lymphocytes.

performed 1 month after completion of six cycles treatment showed complete resolution of peritoneal carcinomatosis, low-attenuation lesions of bilateral ovaries, and ascites. Repeat bone marrow biopsy showed no evidence of residual lymphoma, indicating attainment of complete remission. She was last seen at follow-up 1 year after diagnosis and is completing a 2-year maintenance treatment with rituximab every 2 months.

Discussion

CA-125 remains a valuable biomarker used to differentiate benign from malignant ovarian pathologies despite wide variations in sensitivity and specificity, ranging from 60% to 95% [7—9]. However, CA-125 can be elevated in a number of clinical conditions, most notably with irritation of serous tissues as seen in endometriosis, cirrhosis, or the presence of pleural or peritoneal fluid [10—12]. In the case presented, the CA-125 was most likely elevated because of peritoneal irritation secondary to infiltration by B cell lymphoma. Peritoneal irritation is most commonly secondary to infection and carcinomatosis. Less common causes include pseudomyxoma peritonea, peritoneal lymphomatosis, tuberculosis, diffuse peritoneal leiomyomatosis, and benign splenosis [13]. Peritoneal infiltration by amyloid deposits was described in patients with WM [14,15]. However, congo red stain of peritoneal biopsy in this patient was negative for amyloid deposits.

There is one prior case report published in 2013 that describes a patient with WM and ovarian involvement [16]. In this case report, a 50-year-old woman underwent a hysterectomy with salpingo-oophorectomy for irregular uterine bleeding. A histologic examination of uterine cervix, uterine walls, and fallopian tubes revealed dense lymphoplasmacytic infiltrate that was most pronounced in the ovaries. This is the first case report of WM initially presenting and secondarily involving both ovaries and other gynecological organs. Examination of ovaries was striking with prominent diffuse infiltrate composed of lymphocytes and plasma cells in the medullary location. CD20 was positive and stained the majority of infiltrating cells. CD138 was positive in a significant proportion of infiltrate albeit less than that of CD20. The following were also noted: serum IgA, 0.53 g/L (low); serum IgG, 47 g/L (high); and serum IgM 47 g/L (high). Serum kappa was 1867 mg/L, lambda was 162 mg/L (high), and serum kappa/lambda ratio was 11.5. Although this is the first case report of WM initially presenting and secondarily involving both ovaries and other gynecological organs, there was no description of treatment or patient outcome.

There are a few case reports of hematologic malignancies presenting with an elevated CA-125. One case reported in 2009 described a patient with IgE multiple myeloma who initially presented with high levels of IgE and CA-125, although no mechanism of CA-125 elevation was proposed [17]. A patient with diffuse large B-cell lymphoma presenting with elevated CA-125, initially misdiagnosed as ovarian cancer, has also been described in the literature. In this case, the proposed mechanism of CA-125 elevation was cytokine-stimulated secretion of CA-125 from mesothelial cells rather than peritoneal irritation [18]. Follicular lymphoma has also been reported to present with elevated CA-125 levels [19]. In all of the above stated cases, the CA-125 levels declined with treatment of the primary malignancy. There are several case reports of WM presenting with atypical conditions such as angioedema, pulmonary infiltrations and even mimicking conditions such as interstitial lung disease and angiosarcoma [20—24].

Multiple initial treatment options are available for LPL [25] Decisions should be based on individual patient and disease characteristics. Chemoimmunotherapy combinations with rituximab and cyclophosphamide—dexamethasone, bendamustine, or bortezomib—dexamethasone provide durable responses and are still indicated in most patients. The approval of the BTK inhibitor ibrutinib in the United States and Europe represents a novel and effective treatment option for both treatment-naive and relapsing patients. Active enrollment in clinical trials whenever possible was endorsed by the panel for most patients with LPL. In our patient, bendamustine—rituximab was chosen as upfront therapy for rapid disease control given the fact that the patient had bulky symptomatic disease with imminent risk for clinical hyperviscosity syndrome [26]. We started the patient on a 2-year rituximab maintenance as an observational, nonrandomized, study of 248 patients with LPL who responded to a rituximab-containing regimen showed that these patients had improved progression-free and overall survival after receiving rituximab maintenance [27].

Conclusions

To our knowledge, this is the first documented case of WM presenting with symptoms classically associated with ovarian cancer and a markedly elevated CA-125. The most likely cause of our patient's elevated CA-125 was peritoneal irritation secondary to diffuse infiltration of peritoneum by neoplastic B cells. This case illustrates the need for clinicians to consider a broad differential when evaluating patients presenting with abdominal carcinomatosis.

Conflict of interest

The authors have no conflicts of interest to disclose regarding the publication of this manuscript.

References

[1] Fonseca R, Hayman S. Waldenström macroglobulinaemia. Br J Haematol 2007;138:700—20.
[2] Garcia-Sanz R, Montoto S, Torrequebrada A, de Coca AG, Petit J, Sureda A, et al. Waldenstrom macroglobulinaemia: presenting features and outcome in a series with 217 cases. Br J Haematol 2001;115:575—82.
[3] Coussy F, Chéreau E, Daraï E, Dhombres F, Lotz JP, Rouzier R, et al. Intérêt du dosage du CA 125 dans la prise en charge du cancer de l'ovaire. Gynécol Obstét Fertil 2011;39:296—301.
[4] Grant DJ, Moorman PG, Akushevich L, Palmieri RT, Bentley RC, Schildkraut JM. Primary peritoneal and ovarian cancers: an epidemiological comparative analysis. Cancer Causes Control 2010;21:991—8.
[5] Goff BA, Mandel L, Muntz HG, Melancon CH. Ovarian carcinoma diagnosis. Cancer 2000;89:2068—75.
[6] Olson SH, Mignone L, Nakraseive C, Caputo TA, Barakat RR, Harlap S. Symptoms of ovarian cancer. Obstet Gynecol 2001;98:212—7.
[7] Andersen MR, Goff BA, Lowe KA, Scholler N, Bergan L, Dresher CW, et al. Combining a symptoms index with CA 125 to improve detection of ovarian cancer. Cancer 2008;113:484—9.
[8] American College of Obstetricians and Gynecologists. Practice Bulletin no. 83: Management of adnexal masses. Washington, DC: American College of Obstetricians and Gynecologists; 2007.
[9] Moss EL, Hollingworth J, Reynolds TM. The role of CA125 in clinical practice. J Clin Pathol 2005;58:308—12.

[10] JoP Bilibio, JoSL Cunha-Filho. Serum prolactin and CA-125 levels as biomarkers of peritoneal endometriosis. Gynecol Obstet Invest 2015;81:96.
[11] Zuckerman E, Lanir A, Sabo E, Rosenvald-Zuckerman T, Matter I, Yeshurun D, et al. Cancer antigen 125: a sensitive marker of ascites in patients with liver cirrhosis. Am J Gastroenterol 1999;94:1613—8.
[12] Cass I, Karlan BY. Ovarian cancer symptoms speak out-but what are they really saying? JNCI J Natl Cancer Inst 2010;102:211—2.
[13] Diop AD, Fontarensky M, Montoriol PF, Da Ines D. CT imaging of peritoneal carcinomatosis and its mimics. Diagn Intervent Imaging 2014;95:861—72.
[14] Raffi F, Cerbelaud P, Lerat F, Cuilliere P, Rymer R, Le Bodic L. Peritoneal amyloidosis in Waldenstrom's macroglobulinemia. Gastroenterol Clin Biol 1985;9:950—1.
[15] Raffi F, Lerat F, Cuilliere P, Roudier JM, Le Bodic L, Rymer R. Peritoneal amyloidosis in Waldenstrom's macroglobulinemia. X-ray computed tomographic aspects. J Radiol 1985;66:735—8.
[16] Albawardi AS, Castella A, Almarzooqi SS. Lymphoplasmacytic lymphoma-Waldenström macroglobulinemia: an unusual presentation in ovaries, fallopian tubes and uterine cervix. Int J Clin Exp Med 2013;6:346—50.
[17] Wang M-l, Huang Q, Yang T-X. IgE myeloma with elevated level of serum CA125. J Zhejiang Univ Sci B 2009;10:559—62.
[18] Allen GW, Forouzannia A, Bailey HH, Howard SP. Non-Hodgkin's lymphoma presenting as a pelvic mass with elevated CA-125. Gynecol Oncol 2004;94:811—3.
[19] Anand R, Markman M. Elevated serum CA-125 in a patient with follicular lymphoma and a history of ovarian cancer. Case Rep Oncol 2011;4:172—4.
[20] Amin CJ, Rabinowitz I. An unusual reoccurrence of Waldenstrom's macroglobulinemia as pleural effusions that had a discordant response with treatment. Clin Lab Haematol 2005;27:200—2.
[21] Consuegra A, Marcos PJ, Vázquez R, Pombo J, Debén G, Verea-Hernando H. Diffuse interstitial lung disease as a first manifestation of Waldenström's macroglobulinemia: case report and review of the literature. Arch Bronconeumol (Engl Ed) 2014;50:151—3.
[22] Khanfar A, Trikha A, Bonds R, Jana B. Angioedema with normal C1q and C1 inhibitor: an atypical presentation of Waldenström macroglobulinemia. Int J Hematol 2013;97:654—6.
[23] Spillane EL, Xia Y, Turiansky GW. Atypical cutaneous presentation of Waldenstrom macroglobulinemia: an extensive erythematous patch mimicking an angiosarcoma. Cutis 2008;81:67—8.
[24] Yap JC, Poh SC. Waldenstrom's macroglobulinemia presenting with pleuropulmonary and gastric manifestations. Singapore Med J 1990;31:405—8.
[25] Leblond V, Kastritis E, Advani R, Ansell SM, Buske C, Castillo JJ, et al. Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia. Blood 2016;128:1321—8.
[26] Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lympoma. J Clin Oncol 2005;23:3383—9.
[27] Treon SP, Hanzis C, Manning RJ, Ioakimidis L, Patterson CJ, Hunter ZR. Maintenance Rituximab is associated with improved clinical outcome in rituximab naïve patients with Waldenstrom Macroglobulinaemia who respond to a rituximab-containing regimen. Br J Haematol 2011;154:357—62.