Recurrent ascites in systemic lupus erythematosus treated with rituximab - a case report and review of pseudo-pseudo Meigs' syndrome

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune and inflammatory disease with multisystem consequences. Pseudo-pseudo Meigs' syndrome (PPMS), or Tjalma syndrome, is a newly recognized manifestation of SLE that is characterized by increased CA-125 level, pleural effusion, and ascites without evidence of tumor. PPMS is relatively rare and likely under-recognized. To our knowledge, there are 11 published case reports about PPMS. In nearly half of the PPMS cases, ascites is the initial symptom of SLE. The pathophysiology of this syndrome is not completely understood but thought to be in part due to chronic inflammation, which is supported by symptoms abating with immunosuppression. We report a case of a 20-year-old woman with known SLE who developed recurrent large volume ascites, subsequently leading to the diagnosis of PPMS, requiring rituximab for additional immunosuppression. To our knowledge, this is the first case of using rituximab as a successful treatment for PPMS.

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Case Report

A 20 year-old woman with hypothyroidism on levothyroxine and systemic lupus erythematosus (SLE), positive ANA 1:1280, positive double-stranded DNA (dsDNA) antibody, positive Smith antibody, positive RNP antibody, hypocomplementemia, arthritis, complicated by Class IV lupus nephritis (on hemodialysis), currently treated with mycophenolate mofetil 1500 mg twice daily, hydroxychloroquine 200 mg twice daily, and prednisone 40 mg daily, was admitted for shortness of breath, progressive abdominal swelling with ascites, and recurrent nausea/vomiting. She was previously treated with cyclophosphamide for lupus nephritis several years ago using the National Institute of Health (NIH) protocol dosing regimen. She was also treated with belimumab, which was stopped due to the patient's inability to finance the medication. Prior to this hospitalization, she required several large volume paracenteses for unclear reasons. The nausea/vomiting also caused her to miss two sessions of hemodialysis. On admission, she was afebrile and normotensive, with regular heart rate and rhythm and 98% oxygen saturation on room air. Her physical exam was significant for abdominal distention with a detectable fluid wave and 1+ pitting edema in the lower extremities. Laboratory testing was significant for hypocomplementemia, an elevated dsDNA antibody, an elevated thyroid stimulating hormone (TSH) level, and new nephrotic-range proteinuria, with an increase in urine protein from 0.8 to 13 grams. She required a large volume paracentesis, but the ascetic fluid did not detect spontaneous bacterial peritonitis (SBP). Cytology analysis of the ascetic fluid was negative for malignancy. The patient continued aggressive treatment for thyroid disease.

About 1.5 weeks into her hospitalization, the patient had re-accumulation of ascetic fluid, requiring another large volume paracentesis. A chest X-ray showed a right-sided pleural effusion but no concerning nodules or lymphadenopathy. Due to concern for Meigs' syndrome, a CA-125, CEA and CA 19-9 were checked, with only the CA-125 elevated. Cytology analysis of the ascetic fluid was again negative for malignancy as was a liver biopsy. A transvaginal ultrasound did not demonstrate an ovarian mass, and previous computed tomographic (CT) scans of the abdomen and pelvis did not demonstrate an abdominal mass. Based on the di-

agnosis of new nephrotic-range proteinuria, the patient underwent a renal biopsy which showed Class III + V lupus nephritis, a change from 1 month prior to this admission. Given the presence of pleural effusion, ascites, and elevated CA-125, pseudo-pseudo Meigs' syndrome (PPMS) was considered.

A more aggressive immunosuppression regimen was initiated by adding rituximab and continuing mycophenolate mofetil and prednisone. Rituximab was dosed based on the rheumatoid arthritis protocol with 1000 mg administered at day 1 and day 15 of treatment.[1] Two weeks after the last dose of rituximab, the patient required a paracentesis to remove 2.3 L of fluid. Two weeks after that procedure, a repeat abdominal ultrasound did not demonstrate drainable ascites. Two months after the last dose of rituximab, a repeat abdominal ultrasound again did not demonstrate drainable ascites. Additionally, we obtained repeat serum complement and urine protein levels 2 and 3 months post-rituximab infusion, which demonstrated an improvement in serum C3 levels and improved proteinuria from 13 g to 2 g. The patient will be re-dosed with rituximab at the same dose in 4-6 months and continue mycophenolate mofetil and prednisone for a maintenance treatment regimen.

Discussion

PPMS is characterized by ascites, pleural effusion and an elevated serum CA-125, in a SLE patient without evidence of an abdominopelvic mass.[2-4] It was first described in 2005 by Wiebren Tjalma and is also known as Tjalma syndrome.[2,4] To our knowledge, there are 11 reported cases in the literature (Table 1). Interestingly, PPMS is frequently the presenting feature leading to the diagnosis of SLE, after malignancy is ruled out, as was seen in 6 out of the 12 reported cases (Table 1). The differential diagnosis for PPMS includes Meigs' syndrome, characterized by ascites, pleural effusion and a benign ovarian mass[5,6] and pseudo Meigs' syndrome, defined as the presence of ascites and pleural effusions due to an abdominopelvic malignancy or other benign mass, including struma ovarii, yolk sac tumor, ovarian carcinoma, leiomyoma, tuberculosis and ovarian hemangioma.[7] In both Meigs' and pseudo Meigs' syndrome, the etiology of ascites formation is thought to be due to tumor irritation of the peritoneal wall, leading to leakage of fluid that originated from the peritoneum.[8,9] The mechanism which leads to ascites formation in PPMS has not been delineated but thought to be strongly linked to the inflammatory response of the serosa, with the presence of elevated inflammatory cytokines [*i.e.*, interleukin (IL)-1b, interferon (IFN)-y and vascular endothelial growth factor (VEGF)], clustering plasma cells in the lymph, and immune complex deposition in the vessels of the peritoneum.[5] While each entity in PPMS can occur separately as a result of SLE, the presence of all 3 findings in a patient with SLE is diagnostic of PPMS.

Serositis, including pleural or pericardial effusion or ascites, is not uncommon in SLE. Ascites occurs in SLE in about 8-11% of the time.[4] Causes of ascites in SLE include protein-losing enteropathy (PLE), lupus peritonitis, and lupus nephritis complicated by nephrotic syndrome.[2,8] Our patient did not have symptoms congruent with PLE or lupus peritonitis, but she did have progressive lupus nephritis, leading to nephrotic-range proteinuria. In review of the other PPMS cases, 3 report the diagnosis

Table 1. Summary of the clinical characteristics of pseudo-pseudo Meigs' syndrome reported cases, including disease manifestations, initial and maintenance treatments, and the time to remission.

Cases	Prior SLE dx	Ascitic fluid	Pleural effusion	Pericardial effusion	Pancytopenia	Lupus nephritis	APLS	Initial Tx.	Maint. Tx	Time to remission
Our case	Yes	Trans	Yes	No	No	Yes	No	Steroid RTX	Steroid MMF HCQ	3 weeks
Ahmed *et al.*	Yes	Exud	Yes	No	Unk	No	No	Steroid	Steroid AZA	8 weeks
Schmitt *et al.*	No	Exud	Unk	Yes	Yes	Yes	Yes	Steroid AZA HCQ	Unk	Unk
Tjalma	Yes	Unk	Yes	No	Yes	No	Yes	Steroid AZA	Unk	6 weeks
Dalvi *et al.*	Yes	Chyle	Yes	Yes	No	No	No	Steroid	MMF	Unk
Tansir *et al.*	No	Unk	Yes	Yes	No	Yes	Yes	Steroid CYC	Steroid HCQ	4 weeks
Lee *et al.* (2 cases)	Yes Yes	Unk Unk	Yes Yes	Yes Yes	Yes No	No Yes	Yes Unk	Steroid Steroid CYC	Steroid HCQ MMF	1 week Unk
Bes and Soy	No	Unk	Yes	Yes	No	No	No	Steroid	HCQ	3 weeks
Gao *et al.*	No	Unk	Yes	No	No	No	No	Steroid	Steroid LFL HCQ	8 weeks
Ural *et al.*	No	Exud	Yes	No	Unk	No	No	Steroid HCQ	Unk	8 weeks
McVorra *et al.*	No	Exud	Yes	Yes	No	No	No	Steroid	Unk	Unk

Trans, transudative; Unk, unknown; Chyle, chylous; Exud, exudative; RTX, rituximab; CYC, cyclophosphamide; AZA, azathioprine; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; LFL, leflunomide.

of lupus nephritis with the presentation of PPMS (Table 1). These cases include a new diagnosis of class I (3) and class II (6) lupus nephritis. While these classes are not associated with nephrotic-range proteinuria, another patient had Class V lupus nephritis.[8] Thus, lupus nephritis can lead to ascites and is a complication of PPMS.

Although our patient had uncontrolled thyroid disease, we did not think this was solely responsible for the development of abdominal ascites as her thyroid function tests improved with initiation and titration levothyroxine, without change or resolution of the ascites burden.

CA-125 is a well described ovarian carcinoma tumor marker,[9,10] with low sensitivity and specificity for malignancy.[2,4,9] Its immunoreactivity is low in the tumors found in both Meigs' and pseudo Meigs' cases, but high in the omentum and mesovarium, further supporting its derivation from the peritoneum.[9] Inflammatory cytokines can also interact with mesothelial cells and augment production of CA-125.[9] Increased CA-125 levels occur in connective tissue diseases, as the result of hemodialysis, and in the presence of ascites.[10,11] Thus, our patient has multiple comorbidities and complications that likely contributed to the elevated CA-125 levels and resulted in PPMS.

Although we did not obtain a whole-body positron-emission tomography or CT scan, we feel that the patient was thoroughly evaluated for a malignancy based on the repeated abdominal CT and ultrasound imaging, repeated ascetic fluid sampling, and a liver biopsy. But, we acknowledge that the risk for an occult malignancy still exists.

Use of immunosuppressive medications can lead to PPMS remission, with reduction of ascites, pleural effusion and normalization of CA-125 levels.[2,12] Table 1 denotes the immunosuppressive agents that have been used. For all cases, steroids were used initially, but maintenance therapies varied in each case and more than one agent was often required. Our case is the first to report rituximab use. Rituximab was chosen because it could be an adjunct to ongoing therapies. Additionally, since she has previously received a course of cyclophosphamide, we wanted to avoid another treatment of this medication. Rituximab is generally well tolerated, but patients are at greatest risk for infusion reactions, with other possible side effects including immunosuppression, hypogammaglobulinemia, malignancy, and progressive multifocal leukoencephalopathy. Most patients entered remission 8 weeks after initiating treatment. In our case, we defined remission by no drainable ascites based on repeat abdominal ultrasounds on two consecutive occasions two months apart and an improvement in C3 and proteinuria.

Conclusions

PPMS is an increasingly recognized manifestation of SLE. It should be included in the differential diagnosis of patients with unexplained ascites, pleural effusion, and an elevated CA-125. Once recognized, immunosuppression should be initiated. Rituximab is an immunosuppressive medication that can be used in conjunction with other treatments and may be an option to achieve remission in PPMS.

References

1. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572-81.
2. Ahmed O, Malley T, Kitchen J. A case of pseudo-pseudo Meigs' syndrome. Oxf Med Case Rep 2019;2019:omy136.
3. Schmitt R, Weichert W, Schneider W, et al. Pseudo-pseudo Meigs' syndrome. Lancet (London, England) 2005;366:1672.
4. Tjalma WA. Ascites, pleural effusion, and CA 125 elevation in an SLE patient, either a Tjalma syndrome or, due to the migrated Filshie clips, a pseudo-Meigs syndrome. Gynecol Oncol 2005;97:288-91.
5. Dalvi SR, Yildirim R, Santoriello D, Belmont HM. Pseudo-pseudo Meigs' syndrome in a patient with systemic lupus erythematosus. Lupus 2012;21:1463-6.
6. Tansir G, Kumar P, Pius A, et al. Pseudo-pseudo Meigs' syndrome: a rare presentation of systemic lupus erythematosus. Reumatismo 2019;71:108-12.
7. Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. J Clin Gastroenterol 2011;45:436-41.
8. Lee SY, Lee SW, Chung WT. Severe inflammation may be caused by hyperferritinemia of pseudo-pseudo Meigs' syndrome in lupus patients: two cases reports and a literature review. Clin Rheumatol 2013;32:1823-6.
9. Bes C, Soy M. Pseudo-pseudo Meigs syndrome developed under the leflunomide therapy. Rheumatol Int 2011;31:521-3.
10. Gao F, Xu Y, Yang G. Pseudo-pseudo Meigs' syndrome presenting with a combination of polyserositis, elevated serum CA 125 in systemic lupus erythematosus: A case report. Medicine 2019;98:e15393.
11. Ural UM, Kiliç A, Güngör T, et al. Tjalma's or pseudo-pseudo-Meigs' syndrome: a case report. Clin Exp Dermatol 2008; 33:363-4.
12. McVorran S, Song J, Pochineni V, Abrudescu-Opran A. Systemic lupus erythematosus presenting with massive ascites: a case of pseudo-pseudo Meigs syndrome. Case Rep Rheumatol. 2016;2016:8701763.