



A Case of Tjalma Syndrome Coincidentally Accompanied by an Ovarian Teratoma Successfully Treated with Intravenous Immunoglobulin-G Adjunctive Therapy

Eun-Kyoung Park¹, Seung-Geun Lee¹, Ik Soo Byon², Sun-Hee Lee¹, Seong-Jun Lee¹, Yoon-Jeong Nam¹, Ji-Hye Park¹, Geun-Tae Kim³, Young-Eun Park⁴, Seong-Hu Park⁵, Joung-Wook Lee⁶, Jun-Hee Lee⁷, Seung-Hoon Baek⁷

Department of Internal Medicine, Pusan National University School of Medicine¹, Busan, Department of Ophthalmology, Pusan National University Yangsan Hospital², Yangsan, Division of Rheumatology, Department of Internal Medicine, Kosin University College of Medicine³, Malgeunsem Hospital⁴, Changwon, Young-do Hospital⁵, Busan St. Mary's Medical Center⁶, Department of Internal Medicine, Ilsin Christian Hospital⁷, Busan, Korea

Tjalma or pseudo-pseudo Meigs' syndrome is a clinical condition that is characterized with ascites, pleural effusion, and increased serum CA-125 levels in patients with systemic lupus erythematosus (SLE) without the presence of ovarian tumor. On the other hand, Meigs' and pseudo-Meigs' syndromes represent the same manifestations with ovarian tumor. In this case report, we present a 43-year-old SLE pa-

tient suffering from Tjalma syndrome with the coexistence of incidental ovarian teratoma, who was successfully treated with intravenous immunoglobulin-G adjunctive therapy after inadequate response to surgical excision of the ovarian tumor, steroid, and cyclophosphamide pulse therapy.

Key Words. Systemic lupus erythematosus, Intravenous immunoglobulin, Ascites, Pleural effusion

Introduction

Meigs' and pseudo-Meigs' syndromes are paraneoplastic conditions characterized by ascites, pleural effusion, and increased CA-125 serum levels accompanied by ovarian tumor with resolution of the ascites and hydrothorax after removal of the ovarian lesion (1,2). Meigs' syndrome is associated with benign ovarian fibromas (1). On the other hand, pseudo-Meigs' syndrome occurs in the presence of ovarian teratoma, ovarian carcinoma or leiomyoma. In patients with systemic lupus erythematosus (SLE), there is a similar condition referred to as Tjalma or pseudo-pseudo Meigs' syndrome, which has the systemic manifestations of Meigs' syndrome, but occurs in the absence of an ovarian neoplasm (3). To date, 6 cases of Tjalma syndrome have been reported and immunosuppressive therapy was shown to effectively treat all of these cases (3-8). However, there are few reports of the coex-

istence of an incidental ovarian tumor with the efficacy of intravenous immunoglobulin-G (IVIG) adjunctive therapy refractory to conventional therapy in Tjalma syndrome.

Here, we present a case of Tjalma syndrome coincidentally accompanied by an ovarian teratoma that was successfully treated with IVIG adjunctive therapy.

Case Report

A 43-year-old woman was admitted to our academic rheumatology clinic with complaints of generalized edema, facial rash, and arthralgia lasting for 5 months. She also complained of abdominal distension, a weight gain of 4 kg over 1 month, and generalized weakness. On physical examination, prominent ascites, bilateral pitting edema of the lower extremities, and swelling of proximal interphalangeal joints were detected. Dermatological examination revealed an erythematous malar rash.

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Corresponding to : Seung-Geun Lee, Division of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine, 179, Gudeok-ro, Seo-gu, Busan 602-739, Korea. E-mail : sglee@pnuh.co.kr

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On the first day of admission (day 0), laboratory findings were as follows: white blood cell count (WBC), 4,900/mm³ (lymphocytes 872/mm³); hemoglobin, 13.6 g/dL; platelet count, 208,000/mm³; erythrocyte sedimentation rate, 43 mm/hr; C-reactive protein, 0.44 mg/dL; serum creatinine, 0.58 mg/dL; serum total protein, 4.6 g/dL; serum albumin, 1.8 g/dL; serum lactate dehydrogenase (LDH), 415 IU/L (normal range 218~472 IU/L); anti-nuclear antibody (ANA), 1:1,280 positive (speckled pattern); anti-double stranded DNA IgG, 37.2 IU/mL (normal range 0~20 IU/mL); C3, 32.0 mg/dL (normal range 90~180 mg/dL); C4, 5.4 mg/dL (normal range 10~40 mg/dL); and serum CA-125, 544.4 U/mL (normal range 0~35 U/mL); positive for anti-RNP Ab, anti-Smith Ab, anti-Ro, anti-histone Ab. Rheumatoid factor, anti-cyclic citrullinated peptide Ab, anti-La, anti-cardiolipin IgG and IgM, and lupus anticoagulant were negative. Urine dipstick protein value was negative and urine protein/creatinine ratio was 298.7 mg/g. Taken together, she was diagnosed with SLE (malar rash, arthritis, lymphopenia, positive ANA, and anti-Smith Ab).

Chest radiography showed a right pleural effusion (Figure 1). Thoracentesis was performed on the right side and fluid analysis showed the following results: total protein, 1.6 g/dL; albumin, 1.0 g/dL; LDH, 169 IU/L; and adenosine deaminase (ADA), 10.8 IU/L (normal range 4.3~20.3 IU/L). Staining and cultures for acid-fast bacilli (AFB) were negative. Pleural effusion was consistent with a transudate by Light's criteria. Abdominal and pelvic computed tomography (CT) scanning showed a 3.6-cm left ovarian teratoma, uterine myoma, and ascites (Figure 2). However, no definite peritoneal or bowel wall thickening or liver cirrhosis, which can cause ascites, was noted. A blood interferon gamma release assay was negative. No abnormality was found on colonoscopy and gastroscopy. Ascitic fluid analysis showed a WBC of 105/mm³ (2% neutrophils, 34% lymphocytes, and 64% other cells) and CA-125

levels of 302.2 U/mL; the ADA range was normal, and staining and cultures for AFB were negative. Cytologic examination of the ascitic fluid was negative for malignancy and the serum-to-ascites albumin gradient was 0.6 g/dL. On echocardiography, her ejection fraction was 65% and there was no abnormality except for mild eccentric mitral regurgitation. Fecal alpha-1 antitrypsin (AAT) clearance was 24.7 mL/day, which was within the normal range.

As the patient had left ovarian teratoma, ascites, pleural effusion, and increased serum and ascites CA-125 levels, we initially suspected pseudo-Meigs' syndrome incidentally accompanied by SLE. She consulted a gynecologist for removal of the ovarian teratoma in order to clarify her diagnosis. However, the operation was postponed because of her general medical problems including hypoalbuminemia and ascites. Medical treatment was started with prednisolone at 0.5 mg · kg⁻¹ · day⁻¹, 400 mg of hydroxychloroquine for SLE, and diuretics for as-

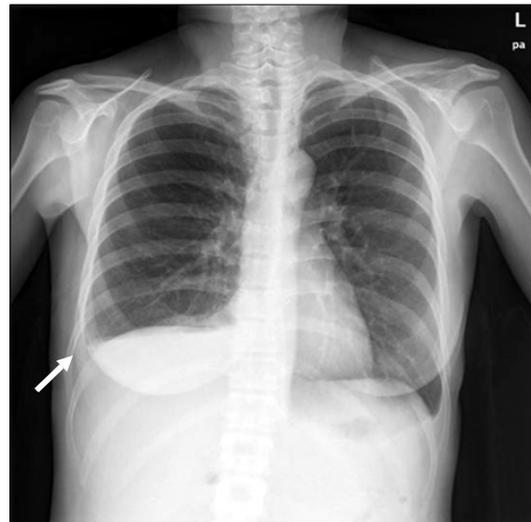


Figure 1. Chest radiograph showing right pleural effusion (arrow).

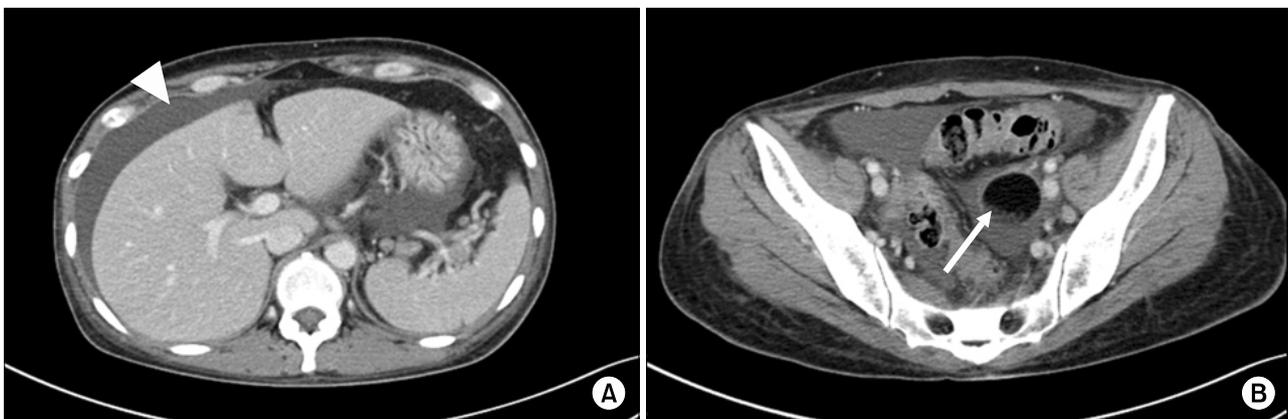


Figure 2. Abdominal computed tomography showing ascites (arrowhead in A) and 4.3 cm sized ovarian tumor (arrow in B).

Table 1. Changes in serum CA-125 and albumin concentrations according to therapy

Day	0	98	102	109	141	143	148	150	154	156	162	178	197
Serum albumin (mg/dL)	1.4	1.5		1.5	1.8			1.6	1.5		2	3.4	3.8
Serum CA-125 (U/mL)	544.4	2,266		1,910	2,951			2,783			1,710	455.1	33.6
Treatment		Oophorectomy			MPT for 3 days			Cyclophosphamide		IVIG for 5 days			

MPT: methylprednisolone pulse therapy, IVIG: intravenous immunoglobulin-G.

cites and pleural effusion. She was discharged on day 22 and medications were maintained in the outpatient department. Her symptoms had not worsened for about 2 months.

Ninety-eight days after her first visit to our clinic (day 98), the patient was readmitted because her peripheral pitting edema had worsened with an additional weight gain of 5 kg. Furthermore, dyspnea had newly developed. A follow-up CT scan showed increased ascites and pleural effusion, and her serum CA-125 levels had increased to 2,266 U/mL (Table 1). Left salphingo-oophorectomy and uterine myomectomy were performed on day 102. A mature teratoma was diagnosed on pathologic examination of the ovarian specimen. Despite elimination of the ovarian tumor, her pleural effusion and ascites did not resolve, and serum CA-125 levels further increased to 2,951 U/mL on day 141 (Table 1). Thus, we assumed that persistent pleural effusion and ascites and increased levels of CA-125 were not caused by the teratoma (pseudo-Meigs' syndrome) but by an autoimmune disease such as SLE (Tjalma syndrome). Thereafter, pulse methylprednisolone therapy on 3 consecutive days given as a 1g intravenous bolus followed by oral prednisolone at $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ was started on day 143. However, her ascites and pleural effusion persisted. Subsequently, on day 148, pulse therapy with 750 mg of cyclophosphamide was added, but her ascites and hypoalbuminemia worsened (Table 1). Thus, we thought that the patient was refractory to this cytotoxic agent and recommend additional treatment. But, she firmly refused other immunosuppressive agents such as mycophenolate mofetil or azathioprine due to fear of adverse events. Based on previous reports of favorable response of various autoimmune conditions to IVIG, therapy with IVIG was discussed with the patient. Her serum IgA levels were 216.3 mg/dL (normal range 70~400 mg/dL); after obtaining the patient's consent, an IVIG infusion (2 g/kg over 5 consecutive days) was performed on day 156. After IVIG administration, her pleural effusion and ascites dramatically resolved. In addition, serum albumin levels increased to 4.2 g/dL, and serum CA-125 levels normalized to 33 U/mL on day 197 (Table 1). Since the IVIG

infusion, she has remained in remission and is being followed up in the outpatient department maintaining low dose prednisolone (2.5 mg/day) and hydroxychloroquine only.

Discussion

We believe that this report represents a case of Tjalma syndrome and implies that SLE was the cause of the patient's ascites, pleural effusion, and elevated CA-125 levels. Initially, an ovarian tumor was indeed found on abdominal CT, leading us to diagnose Meigs' or pseudo-Meigs' syndrome. However, there was no improvement in the patient's systemic findings and serum CA-125 levels after removal of the ovarian tumor, which was histologically confirmed as a well-differentiated teratoma. It is well known that after removal of the causative tumor in pseudo-Meigs' syndrome, ascites invariably improves, and recurrence is rare (1,2). We therefore concluded that the teratoma was a coincidental finding and not the direct cause of her signs. To our knowledge, this is the first reported case of a Tjalma syndrome incidentally accompanied by ovarian teratoma. Although Bes et al. (7) reported Tjalma syndrome with the coexistence of cystic formation in the right adnexal region, this was a misdiagnosis of ovarian malignancy rather than a true ovarian tumor.

Among other diagnostic possibilities, such as constrictive pericarditis, liver cirrhosis, tuberculous peritonitis, and nephrotic syndrome were excluded by echocardiography, abdominal CT scan, microbiologic testing for tuberculosis, and urinalysis findings, respectively. Although protein-losing enteropathy was also a consideration, this condition was excluded for the following reasons. First, AAT clearance was within the normal range (nuclear radiology to quantitate enteric protein loss was impossible in our tertiary hospital). Second, ascites had an exudative nature rather than transudative features, implying that these were not caused by hypoalbuminemia. Third, she had no diarrhea or dyslipidemia and no abnormality on colonoscopy. Acute or chronic lupus peritonitis was another diagnostic consideration. However, acute lupus peritonitis usually presents with severe abdominal pain and evidence of

bowel wall inflammation on imaging, which were not observed in this case. In addition, lupus peritonitis usually does not cause clinically significant ascites (9).

CA-125, a useful biomarker for evaluation of gynecologic tumors, is expressed in mesenchymal cell and increases as a result of interaction between mesothelial cell and cytokines such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (10). CA-125 may be elevated by renal involvement of increased disease activity in SLE, but this finding remains controversial (11). Recently, Yang et al. (11) showed a significant relationship between serositis and elevated serum CA-125 in SLE patients. However, they did not report any patient with massive pleural effusion and ascites in combination with high CA-125 levels. Therefore, we assume that CA-125 elevation in our patient is not caused by "simple" serositis but a manifestation of Tjalma syndrome which is a distinctive clinical entity in SLE.

Treatment of Tjalma syndrome has yet to be established as a result of the limited number of reports of this condition. In previous reports, patients with Tjalma syndrome in whom steroids and other immunosuppressive agents including cyclophosphamide, mycophenolate mofetil, and azathioprine have been employed have been successfully treated with no relapse (3-8). In this case, we initiated IVIG treatment 1 week after steroid and cyclophosphamide pulse therapy as she did not show recovered systemic signs and serum CA-125 levels despite treatment with these immunosuppressive drugs. Just after administration of IVIG infusion over 5 consecutive days, a rapid improvement of all clinical and serologic markers was observed. Because of the relatively short time interval (1 week) between the initiation of immunosuppressive agents and IVIG, it is difficult to determine whether IVIG treatment solely led to clinical remission in this patient. However, we infer that IVIG could have played an adjunctive role in the clinical improvement of her condition considering both the onset of clinical improvement after IVIG treatment and the pharmacokinetics of IVIG. Once administered, IVIG causes an initial sharp rise in serum concentrations followed by a rapid waning for 1~4 days (12), which suggests that the effects of IVIG therapy can be observed rapidly, as in the current case.

There exist many uncertainties as to how immunoglobulin acts although numerous reports of its effectiveness in various autoimmune diseases (12). It is assumed that it would work through Fc receptor blockade, inhibition of complement deposition, enhancement of regulatory T cells, inhibition or neutralization of cytokines and growth factors, accelerated clearance of autoantibodies, modulation of adhesion molecules and cell receptors, and activation of regulatory macrophages

through the Fc γ RIIb receptor (12). IVIG also showed anti-VEGF antibody activity via stimulating the production of IL-12 which has an anti-angiogenic cytokine and inhibiting VEGF mRNA expression (13). We speculated that anti-VEGF antibody activity of IVIG would play a role in our patient, considering that VEGF can stimulate CA-125 expression.

Summary

In conclusion, this case suggests that the combination of ascites, pleural effusion, and elevated CA-125 in patients with SLE should indicate the possibility of Tjalma syndrome, even in the presence of ovarian tumor. Additionally, IVIG adjunctive therapy can be effective for the management of Tjalma syndrome.

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