

Case Report

A case of minimal change nephrotic syndrome complicated by ovarian vein thrombosis

Ayuko YAMASHITA¹, Hideyuki ARAI¹, Kenta TORIGOE^{1,4}, Yoshiaki MURAYA¹, Masahiro NAKASHIMA², Yoko OBATA^{3,4}, Tomoya NISHINO⁴

¹Department of Internal Medicine, Japan Community Health Care Organization, Isahaya General Hospital, Isahaya, Japan

²Department of Tumor and Diagnostic Pathology, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan

³Medical Education Development Center, Nagasaki University Hospital, Nagasaki, Japan

⁴Department of Nephrology, Nagasaki University Hospital, Nagasaki, Japan

The patient was a 54-year-old woman undergoing steroid treatment as a maintenance therapy of remission for minimal change nephrotic syndrome (MCNS). After pain appeared in her right-lower abdomen, an abdominal contrast computed tomography scan revealed thrombosis of the right ovarian vein. Laboratory evaluation on admission revealed proteinuria (3.5 g/day) and decreased serum total protein (4.9 g/dL) and albumin (2.4 g/dL) levels, indicating nephrotic syndrome recurrence. Leukocyte and C-reactive protein levels were elevated; over 100 leukocytes/high power field were detected in the urine, and *E. coli* was detected in both blood and urine cultures, indicating septicemia due to pyelonephritis. The thrombosis disappeared after approximately 27 weeks of heparin and warfarin treatment. The MCNS recurrence was treated with an increased steroid dose; after about 6 weeks, the patient was negative for urinary protein. Her pyelonephritis improved with antibiotic treatment. The patient was discharged in good condition on day 55 after admission. When patients with nephrotic syndrome complain of abdominal pain, venous thrombosis in the abdominal cavity should be considered.

ACTA MEDICA NAGASAKIENSIA 61: 41–44, 2017

Key words: minimal change nephrotic syndrome, ovarian vein thrombosis, pyelonephritis

Introduction

Various mechanisms can lead to thrombosis in nephrotic syndrome, including increased coagulability, loss of coagulation regulatory proteins through the urine, decrease of fibrinolytic proteins, and platelet activation. Complicating thrombosis is present in about 25% of adult nephrotic syndrome cases [1]. It is particularly common in membranous nephropathy, followed by membranoproliferative glomerulonephritis and minimal change nephrotic syndrome (MCNS) [1]. Thrombi tend to occur in deep and renal veins, and re-

ports of thrombosis in ovarian veins are rare. Here we report our experience with a case of MCNS complicated by ovarian vein thrombosis.

Case Report

The patient was a 54-year-old woman with no history of miscarriage and nothing relevant of note in her medical or family histories. Nephrotic syndrome first occurred at 50 years of age, with total protein (TP) concentration of 4.7 g/

Address correspondence: Hideyuki Arai, M.D., Ph.D. Japan Community Health Care Organization, Isahaya General Hospital, 24-1, Eisyohigashi-machi, Isahaya, Nagasaki 854-8501, Japan
TEL: +81-957-22-1380; FAX: +81-957-22-1184; E-mail: hidearai2001@yahoo.co.jp

Received September 9, 2016; Accepted November 16, 2016

dL, albumin (Alb) of 2.4 g/dL, and 24-hour urinary protein level of 4.3 g/gCr. A kidney biopsy revealed that, of 12 glomeruli, most were normal, apart from 1 that was hyalinized and 1 that was collapsed. Based on these findings, the patient was diagnosed with MCNS. Treatment with 8 mg/day methylprednisolone was initiated, which was later increased to 16 mg/day. Following complete remission, the patient was put on a maintenance dose of 6 mg/day.

Four years later, at 54 years of age, the patient was examined as an outpatient at our hospital for right-lower abdominal pain and nausea. A plain abdominal computed tomography (CT) revealed thrombosis in the right ovarian vein, which was confirmed on contrast CT. Blood and urine tests performed that day showed a recurrence of nephrotic syndrome and pyelonephritis, so she was admitted to the hospital for more intensive treatment. At admission, the patient was 156 cm tall and weighed 37.7 kg. She regularly weighed 38 kg; thus, there was no evidence of weight change. Her body temperature was 37.0°C, blood pressure 100/71 mmHg, heart rate 105 beats/min, and SpO₂ 99% (room air). Physical findings revealed no palpebral conjunctiva anemia, no bulbar conjunctiva jaundice, no swelling or tenderness in the cervical lymph nodes, clear respiratory sounds, regular heart sounds with no murmur, a flat and soft abdomen, and good bowel sounds; however, there was tenderness in the right-lower abdomen. No costovertebral angle tenderness was found. Pitting edema was also observed on both lower legs.

Test results at hospital admission (Table 1) indicated nephrotic syndrome, with TP concentration of 4.9 g/dL, Alb of 2.4 g/dL, and 24-hour urinary protein level of 3.5 g/day.



Figure 1: Abdominal contrast CT revealed thrombosis in the right ovarian vein (arrow)

Selectivity index was 0.13. Leukocyte and C-reactive protein (CRP) levels were elevated; over 100 leukocytes/ high power field were detected in the urine, and E. coli was detected in both blood and urine cultures, indicating septicemia due to pyelonephritis. D-dimer level were elevated. Abdominal contrast CT indicated right ovarian vein thrombosis (Fig. 1). Contrast CT did not reveal any obvious thrombi in either pulmonary artery or from the descending vena cava to the deep veins of the lower limbs.

Since the MCNS recurrence and pyelonephritis were observed in addition to the right ovarian vein thrombosis, the treatment addressed all of the concurrent conditions. For right ovarian vein thrombosis, the patient was administered 10,000 units/day unfractionated heparin via continuous intravenous infusion, which was adjusted to extend the activated partial thromboplastin time 2–2.5-fold. Warfarin was

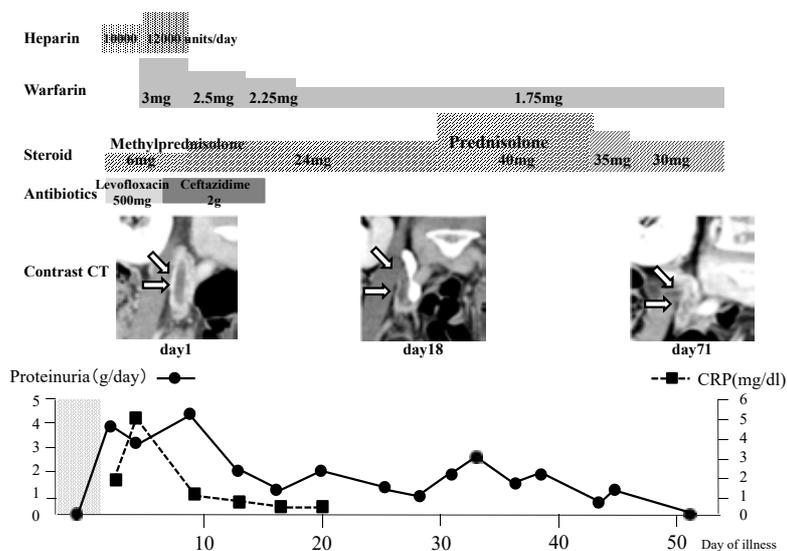


Figure 2: Clinical course

later added and the dose adjusted to attain a prothrombin time-international normalized ratio of 1.5–2.5. The abdominal pain improved on day 3 after admission. Heparin administration was halted on day 6. The ovarian vein thrombosis had shrunk on day 18, and furthermore it had become smaller on day 71 (Fig. 2). The thrombosis completely disappeared about 27 weeks after initiating treatment. The patient was kept on warfarin without recurrence after 2 years. The ovarian vein thrombosis required anticoagulant therapy immediately upon admission, so a repeat renal biopsy was not performed. Since the selectivity index indicated high selectivity, treatment was conducted on the assumption of MCNS recurrence. The methylprednisolone dose was increased from 6 mg/day to 24 mg/day. After 4 weeks, urinary protein levels had declined to 2 g/day, but without complete remission. Therefore, the methylprednisolone treatment was switched to 40 mg/day prednisolone. Urinary protein gradually declined, with complete remission after about 6 weeks. Ceftazidime was administered for pyelonephritis and sepsis, as *E. coli* detected in urine and blood cultures was sensitive to this drug. Levels of CRP and urinary leukocytes improved quickly. The patient was discharged in good condition on day 55 after admission (Fig. 2).

Discussion

This case involved MCNS complicated by ovarian vein thrombosis and pyelonephritis.

Ovarian vein thrombosis is a rare condition. It is more common in pregnancy, occurring in 1/600 to 1/2000 pregnancies [2]. Previously, Wysokinska et al. reported in a series of 35 patients, 34% had an underlying malignancy, 34% assumed hormone therapy, 23% experienced recent pelvic infection, 20% underwent recent abdominal surgery, and 14% had postpartum ovarian vein thrombosis [3,4]. The pathogenesis of ovarian vein thrombosis is attributed to the 3 classic factors that predispose to venous thrombosis: vessel wall injury, venous stasis, and hypercoagulability (Virchow's triad) [5]. Vascular endothelial injury may result from either direct surgical trauma or indirectly from local infection or inflammation. Ovarian vein thrombosis involved the right ovary in 90 % of cases. This is thought to occur due to uterine dextrorotation resulting in increase stasis and longer right ovarian vein with less competent valves. The hypercoagulable state of pregnancy is attributed to elevated coagulation factor levels, increased platelet adhesion, and decreased fibrinolysis [6]. Lower abdominal pain and fever are common symptoms. Diagnosis can be made by contrast CT (sen-

sitivity 100%, specificity 99%) or magnetic resonance imaging (MRI; sensitivity 92%, specificity 100%) [7]. Pulmonary embolism is reported in 25% of untreated cases [2]. In the present case, congenital thrombotic factors were not likely to have led to ovarian vein thrombosis because protein C and S were within normal ranges. In addition, the patient had no relevant prior history, such as malignant tumors or pelvic surgery. Thus, nephrotic syndrome and pyelonephritis were considered the most likely cause.

MCNS occurs frequently in children and is an important disease in Japan, comprising 38.7% of primary nephrotic syndrome cases in adults. It responds well to adrenocortical steroids, and the initial treatment achieves remission in more than 90% of cases [8,9]. Remission rates in adults with MCNS are comparable, but complete remission takes longer in patients 50 years of age or older, as in this case, compared with younger patients [10]. Further, recurrence rates when reducing steroid dose are high (30-70%) [8,9,11], underscoring the need for caution during this time.

There are several mechanisms of thrombosis in nephrotic syndrome, including increased coagulability, loss of coagulation regulatory proteins through the urine, decrease of fibrinolytic proteins, and platelet activation. Thrombosis is a relatively frequent complication in adult nephrotic syndrome, occurring in about 25% of patients [1]. Risk is highest in membranous nephropathy, but has also been reported in cases of membranoproliferative glomerulonephritis and MCNS [1]. Reports of deep vein thrombosis, renal vein thrombosis, and pulmonary artery and vein thrombosis are most common, and we could only find 1 other report on ovarian vein thrombosis [12]. The risk of thrombosis increases in nephrotic syndrome for Alb levels less than 2.0 g/dL [13]; however, in this case, Alb was 2.4 g/dL, indicating that the patient was not at a particularly high risk of thrombosis. Recently, infectious disease has been reported to be a risk factor for venous thrombosis [14], occurring in 2.6% of sepsis cases [15]. In addition, Bassilios et al. reported a case of thrombosis due to acute pyelonephritis, which was also observed in this case [16]. The mechanism is thought to involve endotoxins or lipopolysaccharides from gram-negative bacilli that promote thrombus formation [16]. Therefore, thrombus formation in the right ovarian vein in this case may have been influenced by not only nephrotic syndrome but also inflammation due to pyelonephritis and sepsis. It is notable that the thrombosis occurred only in the ovarian vein in this case. Previously, Wysokinska et al. reported that the patients with pelvic infection, as this case, were more likely to develop ovarian vein thrombosis [4]. Moreover, we consider that early diagnosis and treatment for not only the ovarian

vein thrombosis but also pyelonephritis and nephritic syndrome led to suppress other thrombosis formation in our patient.

There is no consensus treatment for ovarian vein thrombosis; antibiotics and anticoagulants are generally administered. Anticoagulant therapy should be administered continuously for at least for 3–6 months. Thrombi in the renal veins or descending vena cava should be treated as for pulmonary embolism [4]. Moreover, although inferior vena cava (IVC) filters are usually not implanted in cases of ovarian vein thrombosis, they may be used if anticoagulant therapy is not effective [17,18]. In nephrotic syndrome, thrombosis outside the renal veins should be treated as for deep vein thrombosis or pulmonary embolism, with anticoagulant therapy that begins with unfractionated or low-molecular-weight heparin that is later switched to warfarin [19]. In cases of nephrotic syndrome complicated by renal vein thrombosis, IVC filters are sometimes implanted when anticoagulant therapy is contraindicated [20]. In this case, treatment began with heparin and was later switched to warfarin. Since the thrombus was reduced, an IVC filter was not implanted.

In conclusion, we encountered a case of MCNS complicated by ovarian vein thrombosis. When patients with nephrotic syndrome complain of abdominal pain, venous thrombosis in the abdominal cavity should be considered.

Compliance with Ethical Standards

Conflict of interest: The authors have declared that no conflict of interest exists.

Human and Animal Rights: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent: The consent of the patient is taken.

References

1. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol.* 2012; 7:513-520.
2. Harris K, Mehta S, Iskhakov E, Chalhoub M, Maniatis T, Forte F, Alkaied H. Ovarian vein thrombosis in the nonpregnant woman: an overlooked diagnosis. *Ther Adv Hematol.* 2012; 3:325-328.
3. De Stefano V, Martinelli I. Abdominal thromboses of splanchnic, renal and ovarian veins. *Best Pract Res Clin Haematol.* 2012; 25(3):253-264.
4. Wysokinska EM, Hodge D, McBane RD 2nd. Ovarian vein thrombosis: incidence of recurrent venous thromboembolism and survival. *Thromb Haemost.* 2006; 96(2):126-31.
5. Basili G, Romano N, Bimbi M, Lorenzetti L, Pietrasanta D, Goletti O. Postpartum ovarian vein thrombosis. *Journal of the Society of Laparoendoscopic Surgeons.* 2011; 15(2):268-71.
6. Kominariak MA, Hibbard JU. Postpartum ovarian vein thrombosis: an update. *Obstet Gynecol Surv.* 2006; 61:337-342.
7. Dessole S, Capobianco G, Arru A, Demurtas P, Ambrosini G. Postpartum ovarian vein thrombosis: an unpredictable event: two case reports and review of the literature. *Arch Gynecol Obstet.* 2003; 267:242-246.
8. Fujimoto S, Yamamoto Y, Hisanaga S, Morita S, Eto T, Tanaka K. Minimal change nephrotic syndrome in adults: response to corticosteroid therapy and frequency of relapse. *Am J Kidney Dis.* 1991; 17:687-692.
9. Nakayama M, Katafuchi R, Yanase T, Ikeda K, Tanaka H, Fujimi S. Steroid responsiveness and frequency of relapse in adult-onset minimal change nephrotic syndrome. *Am J Kidney Dis.* 2002; 39:503-512.
10. Tse KC, Lam MF, Yip PS, Li FK, Choy BY, Lai KN, et al. Idiopathic minimal change nephrotic syndrome in older adults: steroid responsiveness and pattern of relapses. *Nephrol Dial Transplant.* 2003; 18:1316-1320.
11. Takei T, Koike M, Suzuki K, Shiota S, Itabashi M, Ohtsubo S, et al. The characteristics of relapse in adult-onset minimal-change nephrotic syndrome. *Clin Exp Nephrol.* 2007; 11:214-217.
12. Wang IK, Lee CH, Yang BY, Chang HY, Lin CL, Chuang FR. Low-molecular-weight heparin successfully treating a nephrotic patient complicated by renal and ovarian vein thrombosis and pulmonary embolism. *Int J Clin Pract.* 2005; 147:72-75.
13. Schmidt M, Horvath-Puho E, Thomsen RW, Sorensen HT. Acute infections and venous thromboembolism. *J Intern Med.* 2012; 271:608-618.
14. Cherng SC, Huang WS, Wang YF, Yang SP, Lin YF. The role of lung scintigraphy in the diagnosis of nephrotic syndrome with pulmonary embolism. *Clin Nucl Med.* 2000; 25:167-172.
15. Vardi M, Ghanem-Zoubi NO, Zidan R, Yurin V, Bitterman H. Venous thromboembolism and the utility of the Padua Prediction Score in patients with sepsis admitted to internal medicine departments. *J Thromb Haemost.* 2013; 11:467-473.
16. Bassilios N, Tassart M, Restoux A, Biqot JM, Rondeau E, Sraer JD. Inferior vena cava thrombosis due to acute pyelonephritis. *Nephrol Dial Transplant.* 2004; 19:981-983.
17. Clarke CS, Harlin SA. Puerperal ovarian vein thrombosis with extension into the inferior vena cava. *Am Surg.* 1999; 65:147-150.
18. Sinha S, Roman AS, Cayne NS, Saltzberg S, Rebarber A. Use of a retrievable suprarenal inferior vena cava filter as a primary intervention for postpartum ovarian vein thrombosis: a case report. *J Reprod Med.* 2008; 53:135-137.
19. Glascock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. *J Am Soc Nephrol.* 2007; 18:2221-2225.
20. Greenfield LJ, Cho KJ, Proctor MC, Sobel M, Shah S, Wingo J. Late results of suprarenal Greenfield vena cava filter placement. *Arch Surg.* 1992; 127:969-973.