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Short Communication

Elevation of plasma D-dimer levels associated with rupture of ovarian endometriotic cysts

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ABSTRACT

Objective: The marker for the early diagnosis of endometriotic cyst rupture is unknown. We report a preliminary study designed to evaluate the relationship between plasma D-dimer levels and endometriotic cyst rupture in clinical case series.

Materials and methods: We reviewed the patients' records of endometriotic cyst rupture cases, and the background (i.e., age, body mass index, and parity) and preoperative laboratory assessments (i.e., white blood cell count, levels of serum C-reactive protein, serum CA125, and plasma D-dimer) of the patients were compared with those of unruptured cases.

Results: Emergency surgery cases of endometriotic cyst rupture ($n = 6$) and planned surgery cases of unruptured endometriotic cysts as controls ($n = 16$) were reviewed. Backgrounds of the patients were not significantly different between the two groups. The plasma D-dimer level was significantly higher in the rupture cases (8.5 μg/mL vs. 0.20 μg/mL, $p < 0.001$). Differences in white blood cell count and serum C-reactive protein level, but not serum CA125 level, were found to be statistically significant between groups.

Conclusion: An elevation of plasma D-dimer level is associated with endometriotic cyst rupture.

Introduction

Endometriotic cyst rupture is one of the typical gynecologic emergencies manifested by acute abdominal pain and inflammatory reactions. A marker for the early diagnosis of endometriotic cyst rupture is unknown, partly because of the rarity of the disease. Persistent and intolerable abdominal pain and the complication of intrapelvic infection following retention of the leaked content of the cysts sometimes lead to an emergency surgery, and therefore, its accurate preoperative diagnosis is clinically important. Differential diagnosis from intestinal disease is often necessary since abdominal pain is a major symptom, and adnexitis should also be ruled out. Without imaging tests, the preoperative diagnostic rate of endometriotic cyst rupture (reported in 1970) based on clinical symptoms and physical examinations was as low as 11% [1]. Many cases of endometriotic cyst rupture do not show typical ultrasonographic findings of intraperitoneal fluid and pooling in the pouch of Douglas because the pouch is often tightly closed in the frozen pelvis of endometriosis. Therefore, preoperative diagnosis of ruptured endometriotic cysts may be difficult even when using transvaginal ultrasonography. A high level of serum CA125 after endometriotic cyst rupture has been reported in several studies [2–4]. It has recently been reported that the plasma D-dimer level elevates after the rupture of the endometriotic cyst [5,6]. We report a preliminary study of evaluating the relationship between plasma D-dimer levels and endometriotic cyst rupture in clinical case series.

Materials and methods

Patients' records were obtained for review from Kyorin University Hospital between January 2011 and March 2014. This study was approved by our institutional review board (Kyorin University School of Medicine). In this study, surgically treated cases of endometriotic cyst rupture were included. We excluded cases who received conservative treatment and whose diagnosis was not

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histologically verified. Backgrounds of the patients and their laboratory assessment results were compared between the cases of ruptured and unruptured endometriotic cysts who received the planned surgical treatment.

The patients' background included their age, body mass index, and parity at the time of surgery. The laboratory assessments performed before the surgery included white blood cell (WBC) counts and levels of serum C-reactive protein (CRP), serum CA125, and plasma D-dimer. We routinely measured plasma D-dimer levels as a preoperative screening for deep venous thrombosis. Patients with a plasma D-dimer level of >0.5 μg/mL underwent ultrasonographic or enhanced computed tomography evaluation of leg veins to rule out thromboembolism.

Categorical variables were analyzed using the chi-square test or Fisher's exact test, and continuous variables were analyzed using the Mann–Whitney *U* test. Data were examined using a statistical program (SPSS Statistics ver. 19; IBM, Tokyo, Japan). A p value of <0.05 was regarded as statistically significant. Plasma D-dimer levels of <0.2 μg/mL, which was below the sensitivity of the STA Liatest D-dimer assay (latex agglutination test; Roche Diagnostics Japan, Tokyo, Japan), were treated as 0.2 μg/mL in our statistical analyses [7].

Results

Emergency surgery cases of endometriotic cyst rupture ($n = 6$) and planned surgery cases of unruptured endometriotic cysts as controls ($n = 16$) were included and reviewed in this study. None of the participants were pregnant at the time of surgery. There were no significant differences in the patients' backgrounds between the rupture and unruptured groups (Table 1).

Endometriotic cyst rupture was clinically suspected in all emergency surgery cases during the preoperative period. High-grade fever was present in only one patient. On physical examination, all patients demonstrated abdominal tenderness, while only one patient had rebound tenderness. According to transvaginal ultrasonographic evaluation, we observed pooling in the pouch of Douglas in one patient and a hypoechoic region around the ovarian cysts instead of the pouch of Douglas in five patients.

Plasma D-dimer level was significantly higher in the rupture cases (Table 1). All the rupture cases had a plasma D-dimer level of >1.5 μg/mL, while in none of the unruptured cases the level exceeded 1.0 μg/mL. Prothrombin time and activated partial thromboplastin time were measured simultaneously with plasma D-dimer level, and found to be within the normal range in all patients. Plasma D-dimer levels returned to normal in all patients postoperatively. Differences in WBC count and serum CRP levels were also found to be statistically significant. Serum CA125 level was not significantly different between the two groups.

Table 1
Comparison of the characteristic factors between unruptured and ruptured cases.

	Unruptured ($n = 16$)	Ruptured ($n = 6$)	p
Age	37.1 ± 4.2	36.2 ± 5.9	0.99[a]
Body mass index (kg/m^2)	21.6 ± 3.6	20.0 ± 1.2	0.37[a]
Nullipara (%)	13 (81)	3 (50)	0.28[b]
Bilateral ovarian cysts (%)	6 (38)	2(33)	0.63[b]
WBC count (×1000/μL)	5.1 ± 1.3	10.8 ± 3.4	0.001[a]
Serum CRP (mg/dL)	0.1 ± 0.1	9.4 ± 5.4	<0.001[a]
Serum CA125 (U/mL)	86.1 ± 87.5	163.6 ± 126.4	0.12[a]
Plasma D-dimer (μg/mL)	0.3 ± 0.2	2.8 ± 1.4	<0.001[a]

CRP = C-reactive protein.
[a] Mann–Whitney *U* test.
[b] Fisher's exact test.

Discussion

D-dimer is a secondary product degraded by plasmin from polymerized fibrin after blood coagulation. A high plasma level of D-dimer usually indicates active fibrinolysis, activated either primary or secondary to clot formation. Endometriosis is a common, benign, and chronic gynecologic disorder, which is defined as the presence of endometrial glands and stroma at extrauterine sites. The ovary is a representative site of ectopic endometrial implants. The fluid in the ovarian endometriotic cysts is derived from periodic bleeding from the endometriotic focus and contains many coagulation products. It is speculated that the leaked content from ruptured endometriotic cysts containing fibrin-degraded products is promptly absorbed through the peritoneal surface and causes a rapid elevation of D-dimer levels in the blood. Fujiwara et al [5] proved the disposition of D-dimers in the endometriotic cyst wall using immunohistochemical methods, which suggests the presence of D-dimer in the cystic fluid.

A high level of serum CA125 was also reported in cases of endometriotic cyst rupture; however, this marker is not specific because it is usually elevated in endometriosis even in unruptured cases [8,9]. We were not able to determine a significant difference in serum CA125 level between the ruptured and unruptured cases. Inflammation of the peritoneum was believed to cause the significant elevation in WBC counts and serum CRP levels in the rupture cases.

It is necessary to rule out other diseases causing an elevation of plasma D-dimer levels, such as venous and arterial thromboembolism, surgery, trauma, malignancy, pregnancy, and disseminated intravascular coagulation [10,11]. We screened five of eight patients, who had plasma D-dimer levels >0.5 μg/mL, for deep venous thrombosis by ultrasonographic or enhanced computed tomographic evaluation. None of the patients were found to be positive for deep venous thrombosis. None of the patients in the study were complicated by thromboembolism in the perioperative period. D-dimer levels have previously been shown to increase in cases of malignant ovarian tumors [12,13]. According to histological analyses, the surgically resected specimens in this study were not malignant. Normal results of prothrombin time and activated partial thromboplastin time in all patients contradict the presence of disseminated intravascular coagulation.

Only a small proportion of the patients showed the typical symptoms and signs (i.e., high-grade fever and rebound tenderness). We found the typical ultrasonographic finding of pooling in the pouch of Douglas in only one patient. Patients with a small amount of leakage or with a frozen pelvis may not show intraperitoneal fluid retention during standard imaging, which makes it difficult to diagnose these patients preoperatively. An elevation of plasma D-dimer levels may be a useful diagnostic marker in these microrupture cases.

Two case reports have described an elevation of D-dimer levels after endometriotic cyst rupture [5,6]. To our knowledge, this is the first preliminary report of an association between endometriotic cyst rupture and elevation of D-dimer levels in a case series, comparing with the unruptured cases. Limitations of this study include its retrospective nature, small sample size, and the fact that it was conducted at a single institution. Future studies should be conducted using a larger number of cases to validate the utility of plasma D-dimer levels as a diagnostic marker for endometriotic cyst rupture.

In conclusion, an elevation of plasma D-dimer level is associated with endometriotic cyst rupture. It may be useful to measure plasma D-dimer levels in combination with general inflammation markers (i.e., WBC count and serum CRP levels) for an early

diagnosis of endometriotic cyst rupture and to determine if emergency surgery is required.

Conflicts of interest

The authors have no conflicts of interest, sources of financial support, corporate involvement, and patent holdings.

References

[1] Pratt JH, Shamblin WR. Spontaneous rupture of endometrial cysts of the ovary presenting as an acute abdominal emergency. Am J Obstet Gynecol 1970;108:56–62.
[2] Johansson J, Santala M, Kauppila A. Explosive rise of serum CA125 following the rupture of ovarian endometrioma. Hum Reprod 1998;13:3503–4.
[3] Kurata H, Sasaki M, Kase H, Kase H, Yamamoto Y, Aoki Y, et al. Elevated serum CA125 and CA19-9 due to the spontaneous rupture of ovarian endometrioma. Eur J Obstet Gynecol Reprod Biol 2002;205:75–6.
[4] Gocmen A, Karaca M, Tarakcioglu M. A ruptured ovarian endometrioma mimicking ovarian malignancy: case report. Eur J Gynaecol Oncol 2003;24:445–6.
[5] Fujiwara H, Kosaka K, Hamanishi S, Hiraka J, Higuchi T, Tatsumi K, et al. Acute elevation of plasma D-dimer levels associated with rupture of an ovarian endometriotic cyst: case report. Hum Reprod 2003;18:338–41.
[6] Uharcek P, Mlyncek M, Ravinger J. Elevation of serum CA125 and D-dimer levels associated with rupture of ovarian endometrioma. Int J Biol Markers 2007;22:203–5.
[7] Waser G, Kathriner S, Wuillemin WA. Performance of the automated and rapid STA Liatest D-dimer on the STA-R analyzer. Thromb Res 2005;116:165–70.
[8] Barbieri RL, Niloff JM, Bast Jr RC, Scaetzl E, Kistner RW, Knapp RC. Elevated serum concentrations of CA-125 in patients with advanced endometriosis. Fertil Steril 1986;45:630–4.
[9] Koninckx PR, Muyldermans M, Meuleman C, Cornillie FJ. CA 125 in the management of endometriosis. Eur J Obstet Gynecol Reprod Biol 1993;49:109–13.
[10] Moresco RN, Vargas LC, Voegeli CF, Santos RC. D-dimer and its relationship to fibrinogen/fibrin degradation products (FDPs) in disorders associated with activation of coagulation or fibrinolytic systems. J Clin Lab Anal 2003;17:77–9.
[11] Horan JT, Francus CW. Fibrin degradation products, fibrin monomer and soluble fibrin in disseminated intravascular coagulation. Semin Thromb Hemost 2001;27:657–66.
[12] Rella C, Coviello M, De Frenza N, Falco G, Chiuri E, Colavito P, et al. Plasma D-dimer measurement as a marker of gynecologic tumors: comparison with Ca 125. Tumori 1993;79:347–51.
[13] Den Ouden M, Ubachs JM, Stoot JE, Van Wersch JW. Thrombin-antithrombin III and D-dimer plasma levels in patients with benign or malignant ovarian tumours. Scand J Clin Lab Invest 1998;58:555–9.