Acute elevation of plasma D-dimer levels associated with rupture of an ovarian endometriotic cyst: Case report

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A clinical case that suggested the involvement of blood coagulation cascades in the inflammation reaction induced by leakage of ovarian endometriotic cysts was encountered. Here, a rapid elevation in plasma D-dimer level (119.6 μg/ml) was observed within 5 h after onset of ovarian cyst rupture. By contrast, the plasma fibrinogen level fell below normal range (105 mg/dl). During the following few days, the plasma D-dimer level fell acutely to approximately normal, while the fibrinogen level gradually increased to a high value (590 mg/dl). In addition, the anti-thrombin III level was slightly reduced on the day after rupture, though the concentration of blood platelets remained unchanged. Three days later, laparoscopic surgery showed the surface of the posterior wall of the uterus and peritoneum of the pelvic wall to be extensively covered with the leaked content of a right ovarian endometriotic cyst. Pathological examination confirmed the diagnosis of endometriotic cyst. In the endometrial stromal region, deposit of D-dimer was detected by immunohistochemical staining. These findings suggest that fibrin-derived degradation products in endometriotic cysts can affect coagulation cascades when they leak into the peritoneal cavity; they may also induce local inflammatory reactions, causing pelvic pain and/or extension of the endometriotic lesion.

Key words: D-dimer/endometriotic cyst/fibrinogen/rupture

Introduction

The rupture of an endometriotic cyst is one of the representative acute gynaecological disorders that are manifested by acute abdominal pain and inflammatory reactions (Pratt and Shamblin, 1970). However, the precise mechanisms causing inflammation, the natural course of the evoked inflammation and/or its contribution to endometriosis remain unknown. A recent study reported that CA-125 levels are elevated after endometriotic cyst rupture (Johansson et al., 1998); however, this marker is not suitable for the early diagnosis of rupture as the assay of serum CA-125 takes a few days to complete. Here, we report the case of a woman with a ruptured ovarian endometriotic cyst who showed a rapid and transient increase in plasma D-dimer level, along with changes in other parameters of the coagulation cascade.

Case report

A 35-year-old Japanese woman consulted the authors’ hospital with a chief complaint of infertility. Transvaginal ultrasonography and magnetic resonance imaging examinations showed that she had an endometriotic cyst of 4×5 cm in size in the right ovary. At 08:15 on the 15th day of the next menstrual cycle, she experienced sudden right lower abdominal pain and visited the hospital at 09:40. On bimanual pelvic examination, severe tenderness was detected around the right ovarian cyst; in addition, highly echogenic peritoneal fluid in the cul-de-sac and a pre-ovulatory follicle in the left ovary were observed using transvaginal ultrasonography. Although laboratory examination showed parameters of inflammation such as C-reactive protein (CRP, 0.1 mg/dl) and white blood cell (WBC) count (4.1×10⁹/l) to be within the normal range, the patient’s abdominal pain became progressively worse. The woman was admitted to hospital with a suspected right ovarian endometriotic cyst rupture. After admission, fever and acute elevation of WBC count (15.0×10⁹/l) were noted at 12:30, and administration of piperacillin (2 g, twice daily) was started. In addition, a very high level of plasma D-dimer (119.6 μg/ml), assayed using a latex photometric immunoassay-angiotensin-converting enzyme assay kit (LPIA ACE D-D dimer kit; DIA-IATRON Co. Ltd, Tokyo, Japan) was detected, together with a slight decrease in plasma fibrinogen level (105 mg/dl). On the following day, an increased serum level of CRP (9.8 mg/dl) was observed. However, the abdominal pain was largely
relieved, the fever had abated, and the plasma D-dimer level had fallen almost to normal (0.9 μg/ml). Changes in these parameters are shown in Figures 1 and 2.

At 3 days after admission, the patient underwent laparoscopic surgery. The posterior surface of the uterus and peritoneal surface of the pelvic cavity, were extensively covered with chocolate-like, dirty fragile tissues. The leaking site of the ovarian cyst was adherent to the right pelvic wall. A right ovarian cystectomy was performed, followed by bipolar electrocoagulation of the endometriotic lesion. Pathological examination verified that the resected ovarian cyst wall was an endometriotic cyst rich in small vessels (Figure 3).

Immunohistochemistry

Immunohistochemical double staining of the removed ovarian endometriotic cyst was performed. The frozen sections were prepared for the detection of D-dimer. Each specimen was embedded in OCT compound (Tissue-Tec; Miles Scientific, Naperville, IL, USA), snap-frozen in liquid nitrogen, and stored at −80°C. Frozen tissues were sectioned (6 μm) using a cryostat microtome (Cryocut 1800; Reichert-Jung, Heidelberg, Germany), immediately air-dried on neoprene (Nisshin EM, Tokyo, Japan) -coated glass slides and fixed in acetone at −20°C for 5 min. The slides were incubated for 30 min at room temperature with mouse anti-human D-dimer monoclonal antibody (mAb, 5 μg/ml; clone DD-3B6/22, IgG1 class, American Diagnostica, Inc.), which specifically reacts with human D-dimer (Whitaker et al., 1984) or a mouse IgG1 negative control mAb (5 μg/ml). The slides were washed, mounted with Perma Fluor Aqueous Mounting Medium (Immunon, Pittsburgh, PA, USA), which reduces fluorescence fading, and then examined under a confocal laser scanning microscope (Carl Zeiss, Inc., Jena, Germany). The deposition of D-dimer was clearly detected in the endometrial stromal region beneath the endometrial epithelial cells that expressed cytokeratin (Figure 4).

Discussion

The rupture of an ovarian endometriotic cyst occasionally presents as an acute abdominal attack (Pratt and Shamblin, 1970). This frequently induces elevations in body temperature, WBC count and serum CRP level, all of which are acute inflammatory reactions. These inflammatory responses are considered to be induced by the content of an ovarian endometriotic cyst. Since abdominal pain is a major symptom, differential diagnosis from intestinal disease is often necessary, and infectious diseases in the adnexa should also be ruled out. Recently, CA-125 levels were reported to rise immediately after the rupture of an endometriotic cyst (Johansson et al., 1998), although in the present patient serum levels of both CA-199 and CA-125 were elevated. As these elevations are continued for several days, these tumour markers serve as excellent parameters for endometriotic cyst rupture, especially when patients do not visit the hospital until a few days after the onset of pain. A problem arises however because assays to monitor these markers normally take several days to complete, and so they are unsuitable for making an early diagnosis.
The present case showed a rapid increase in plasma D-dimer level, which reached >100 μg/ml. D-dimer is a secondary product that is degraded by plasmin from polymerized fibrin after the process of blood coagulation. As a result, a high plasma level of D-dimer indicates highly active and excessive blood coagulation, while the dimer is degraded in blood vessels throughout the body. In general, D-dimer is used as a clinical parameter to monitor disseminated intravascular coagulation (DIC) (Horan and Francis, 2001), and a high level—as was seen in the present patient—is seldom encountered, except in rare cases of severe DIC. The sensitivity range of the D-dimer assay kit is ≤20 μg/ml. Usually, the plasma D-dimer level does

Figure 3. Haematoxylin and eosin staining of the removed ovarian cyst wall. The cyst wall was lined with endometrial epithelial cells (EEC). Beneath this layer, endometrial stromal cells were observed. This stromal layer contained small vessels (arrows).

Figure 4. Double staining of the resected ovarian cyst wall using anti-cytokeratin antibody (green-stained by FITC) and anti-D-dimer antibody (red-stained by rhodamine). (A) Anti-D-dimer mAb; (B) negative control mouse mAb. D-dimer was diffusely detected (arrows) beneath the endometrial epithelial cells (EEC).
not exceed 100 μg/ml, even in cases with acute onset of leukaemia or with a major embolism. Laboratory data relating to the coagulation cascade have shown different patterns compared with DIC (Mammen, 2000). In the present patient, as very little change in platelet concentration was observed, it is unlikely that abundant intravascular coagulation had occurred. The plasma D-dimer level may also be elevated when blood coagulation occurs, and after its degradation in an isolated compartment such as a haematoma. Subsequently, the accumulated coagulation-related products may enter the blood circulation in some way. Although it has been reported that plasma D-dimer levels are elevated in cases of, for example, intracranial haemorrhage or huge intramuscular haematoma (Fujii et al., 2001; Hoffmann et al., 2001), the plasma D-dimer level is normally not high, probably because the inflow of haemorrhagic contents into the blood circulation is limited in most cases. In this respect, ovarian endometriotic cyst is a unique pathological condition, due to the large amount of coagulation-related products that are derived from periodical bleeding of the cyst which, when rupturing while facing the peritoneal cavity, can scatter its contents rapidly and extensively through the free peritoneal space. Thus, it is reasonable to consider that the leaked content of endometriotic cyst contained fibrin-degraded products (including D-dimer), followed by prompt absorption of these products through the peritoneal surface, led to an elevation of D-dimer levels in blood. To our knowledge, the deposition of D-dimer in the endometriotic cyst wall is a novel finding, indicating prior coagula formation in the cyst, and strongly suggesting the presence of D-dimer in the cyst fluid to support our interpretation.

On the day of onset, although it was supposed from clinical findings that the patient’s lower abdominal pain was due to ovarian endometriotic cyst rupture, there was uncertainty as to whether emergency surgery should be performed, mainly because no published information was available about the relationship between cyst rupture and D-dimer. As the safety of emergency surgery could not be ensured in the presence of this apparently abnormal data on coagulation cascades, the decision was made to observe the patient conservatively, and to seek any symptom indicating the presence of another critical disease causing plasma D-dimer elevation. Fortunately, no serious disease was apparent, and the patient’s general condition and laboratory data returned to near-normal within a few days. This suggested that the episode was caused by transient leakage of endometriotic cyst fluid, and not by other critical diseases.

The plasma fibrinogen level in this patient returned to normal after she had recovered from this episode, indicating that the low level of fibrinogen on the day of onset of abdominal pain reflected a sudden decrease in fibrinogen level. Anti-thrombin III (AT-III) was also affected by the episode, and both prothrombin time (PT) and partial thromboplastin time (PTT) were slightly changed during the period (data not shown). These findings suggest that the contents of an ovarian cyst can induce coagulation reactions. Consequently, the coagulation cascade might be involved in a local reaction in those peritoneal tissues that are in direct contact with the endometriotic cyst contents. This reaction, in theory, stimulates inflammation to evoke pelvic pain by producing biologically active molecules such as cytokines and prostaglandins (Lampugnani and Donati, 1987; Csala et al., 1998). Recent studies have shown that fibrin degradation products directly promoted smooth muscle cell outgrowth (Naito et al., 2000), and that endometriotic cyst fluid had a growth-enhancing effect on endometrioma cells (Badawy et al., 1998). Thus, the present case provided an important suggestion for the mechanisms of inflammation induced by rupture of endometriotic cyst, as well as some roles of fibrin degradation products in extension of endometriosis.

Notably, a rapid change in plasma D-dimer level was observed immediately after the onset of pain. At present, there are no definitive parameters indicating which cases of endometriotic cyst rupture should undergo surgery and which should be treated conservatively. However, this assessment becomes increasingly important if the patient is concerned about future fertility. Based on the above speculation elicited from this case, D-dimer may become one of several parameters used to evaluate the risk of extending the endometriotic lesion and inflammatory reactions. In this respect, further studies should be conducted to validate the relevance of D-dimer to endometriotic cyst rupture, and to determine the sensitivity and specificity of its measurement in clinical cases.

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References

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D-dimer elevation in endometriotic cyst rupture