Acute inflammation in the uterine isthmus coincides with postpartum acute myometritis in the uterine body involving refractory postpartum hemorrhage of unknown etiology after cesarean delivery

博士（医学）　Divyanu Jain

論文題目

Acute inflammation in the uterine isthmus coincides with postpartum acute myometritis in the uterine body involving refractory postpartum hemorrhage of unknown etiology after cesarean delivery

(帝王切開術後に生じた原因不明の難治性分娩後出血症例における、後産期急性子宮体部筋層炎を合併した子宮峡部の急性炎症)

論文の内容の要旨

[Introduction]

Postpartum hemorrhage (PPH) is one of the leading causes of maternal death worldwide, followed by hypertensive disorders and sepsis. Even in developed countries such as Japan, obstetric hemorrhage is the most frequent cause of maternal death. There are a number of causes of PPH, among which uterine atony alone accounts for approximately 80% of all cases. We recently reported the histopathological characteristics of a uterus with refractory atony of unknown etiology, namely, the diffuse degranulation of mast cells, increased expression of complement C5a receptor (C5aR), and massive infiltration of macrophages and neutrophils into the uterine body and termed it as postpartum acute myometritis (PAM). In this study, we focused on the uterine isthmus just adjacent to the body. Cesarean incision is usually carried out at the lower uterine segment, which is anatomically similar to the uterine isthmus and is directly exposed to amniotic fluid during cesarean delivery. The aim of this study was to histologically examine the uterine isthmus in cases of PAM in the uterine body after cesarean delivery.

[Materials and Methods]

Hamamatsu University School of Medicine is the national registration center for amniotic fluid embolism (AFE) in Japan. Cases throughout Japan were registered in accordance with the entry criteria for the Japan AFE registry. Uterine samples obtained between 2011 and 2017 were included in the present study. We excluded cases showing placental abruption, placenta accreta, placenta previa, multiple gestation, chorioamnionitis, uterine or cervical laceration, and sepsis with disseminated intravascular coagulation. PAM was diagnosed in the uterine body with the pathological criteria as described in our previous study. In the present study, we enrolled five available isthmus tissues from uteri obtained by abdominal hysterectomy due to PPH during cesarean section and PAM positive in body. Control tissues were obtained from pregnant patients (n=15) registered at our university hospital. Uterine body and isthmus tissue biopsies were taken from the uterine corpus and inferior border of the lower

uterine segment incision site, respectively. Tissues were all fixed in formalin and embedded in paraffin. Immunohistochemistry was performed for the following inflammatory cell markers: tryptase for mast cells, CD68 for macrophages, neutrophil elastase for neutrophils, and the T-cell marker CD3. Numbers of positively stained cells were counted on digital images and analyzed using Winroof Image Analysis Software. Statistical analysis was performed. The Ethics Committee of Hamamatsu University School of Medicine approved all of the procedures performed in the present study (No. 15-333 and 16-165) and written informed consent was obtained from all cases.

[Results]

The massive infiltration of inflammatory cells in the isthmus tissue of PAM-positive bodies was observed along with significant interstitial edema in hematoxylin and eosin (HE)-stained isthmus tissue sections, whereas control tissue sections did not show any inflammatory cell infiltrates or interstitial edema. Immunohistochemistry for CD3-positive T cells showed no staining in either group. In the isthmus tissues of PAM-positive bodies, the majority of mast cells showed a characteristic large ‘Halo’ of tryptase positivity that clearly indicated mast cell activation and degranulation. On the other hand, the control group had few tryptase-positive mast cells with a halo. The number of tryptase-positive mast cells was significantly higher in the isthmus tissues of PAM-positive bodies than in those of the control. Elastase-positive neutrophils were massively dispersed in the isthmus tissues of PAM-positive bodies, but not in those of the control. The number of elastase-positive neutrophils and CD68-positive macrophages infiltrating the isthmus tissues of PAM-positive bodies was significantly higher than that in control isthmus cases. Significantly higher number of C5aR-positive cells were observed in the isthmus tissues of PAM-positive bodies, but not in those of the control.

[Discussion]

This is the first histopathological study on uterine atony with PPH of unknown etiology that investigated an important yet overlooked part of the uterus, the isthmus. The study revealed that anaphylactoid reaction-associated inflammation was observed in the uterine body as well as isthmus, in cases of sudden refractory uterine atony after cesarean delivery. The results provide an indirect, but somewhat relevant insight into the relationship between the exposure of the myometrial cesarean incision to amniotic fluid and the initiation of an acute anaphylactoid reaction in the uterus, however direct evidence in this regard has not been reported. Anaphylactoid reaction-associated inflammation in the uterine isthmus is not a normal physiological state and may induce a malfunction in the uterine isthmus, such as subinvolution of the gravid uterus, at least partly, might also contribute to the exacerbation of refractory PPH.

[Conclusion]

Acute inflammation and an anaphylactoid reaction were histologically detected not only in the uterine body, but also in the isthmus among cases of refractory PPH of unknown etiology after cesarean section.