Previous studies based on equine endometrial biopsy (EB) have shown that microscopic pathologic changes involving fibrosis and atrophy in the endometrium are a major cause of subfertility and reduction of the foaling rate (FR) in brood mares [10–12, 19]. These irreversible pathologic changes in the uterus have been designated as chronic degenerative endometritis [10], endometrial fibrosis [12] and chronic degenerative endometrial disease [19].

At an international workshop conducted in the United Kingdom in August 1992, the above terms were reclassified under the compound term “endometrosis” or “equine endometrosis” (EE), which comes from ancient Greek (endos=inside, metra=womb, –osis=disease), with the new term referring to a degenerative disease characterized by...
stromal endometrial fibrosis (SEF) accompanied by endometrial atrophy, periglandular fibrosis (PF) (the so-called “nest” or “fibrotic nest”), lymphatic lacunae (LL) and reduction in the number of uterine glands [1]. Furthermore, recent progress in research indicates that both angiogenesis and angiopathy [4, 21] and endometrial maldifferentiation [6] should be taken into account in the histopathological diagnosis of EE as important findings [22]. There is no relationship between EE and the human disease “endometriosis.”

The onset and severity of EE are closely related to the age of the mare, although parity and chronic inflammation may also play a role in the etiopathogenesis [3, 6, 19]. However, neither seasonal and/or cyclical endocrine variations nor bacterial infection and/or repeated inflammation appear to have a major influence on the onset of EE [6, 9]. At the present time, EE is considered to be a collective disease entity comprising progressive, irreversible, regenerative and degenerative conditions of the equine endometrium that aggravate the severity and extent of the pathologic changes associated with aging [1]. Although EB is a relatively easy and safe technique, it is still unclear whether a single EB specimen is representative of the entire endometrial morphology when estimating FR [2, 27] because there is no agreement on whether EE lesions are widespread and diffusely distributed throughout the endometrium or distributed locally as focal lesions [2, 12, 27]. In most cases, the diagnosis of EE is based on evaluation of a single endometrial biopsy; few studies using specimens from the entire endometrium have been conducted. In addition, few studies of EE have been conducted in Thoroughbred mares in Japan [7].

The purpose of the present study was to investigate the characteristics of EE in Thoroughbred mares in Japan using histologic examination, and to clarify the distribution pattern of the characteristic lesions of EE in the entire uterus.

**Materials and Methods**

The specimens used in this study were obtained from fifty nonpregnant Thoroughbred mares, ranging in age 1 year old to 30 years old (Table 1; 16 maiden mares and 34 mares at least 2 weeks postpartum), that had been raised in Hidaka District, Hokkaido, Japan, and had died, in some cases suddenly, or had been euthanized because of spontaneous colic or catastrophic musculoskeletal injury. Immediately after death, the reproductive tracts of the mares were examined macroscopically. Only macroscopically normal uteri were recovered and used for the study. Uteri were obtained at all stages of the estrus cycle at the time of slaughter, as confirmed from observations of the surface and mid-sagittal sections of the ovaries. Endometrial samples (approximately 4 cm²) were taken as transverse sections from nine uterine sites in total (one sample per site), including the cranial uterine horns, the mid-portion of the right and left uterine horns, the caudal uterine horns, the uterine horn-body junction, the mid-portion of the uterine body and the area adjacent to the internal uterine orifice (Table 1). Tissue was fixed in 10% neutral buffered formaldehyde, embedded routinely in paraffin wax and cut into sections 4 µm thick. Sections from each site were then rinsed and stained with hematoxylin-eosin (HE), elastica van Gieson (EVG) and periodic acid-Schiff (PAS) and examined using light microscopy. Based on the morphologic characteristics of EE classified in terms of Kenney categories [12], samples were defined as showing EE when one or more of the following histopathologic features were observed in samples from any one of the nine sites: (1) SEF, (2) PF, (3) cystic distension of glands, (4) LL derived from dilated lymphatic vessels in the lamina propria and (5) endometrial cysts (ECs) protruding into the uterine lumen. Taking the classification of age of mares estimated by Vanderwall and Woods [26] into consideration, the fifty cases were divided into three distinct age cohorts: group A (1–6 years, 17 cases), group B (7–12 years, 16 cases) and group C (13–30 years, 17 cases) (Table 1). The association between EE diagnosis at the nine uterine sites and age group was analyzed using Mantel extension.

For transmission electron microscopy (TEM), formalin-fixed uterine tissue specimens were collected from four mares aged 3 (Table 1; No. 9), 4 (No. 11), 25 (No. 48) and 30 (No. 50) years, respectively, and then the specimens were postfixed with 2.5% glutaraldehyde and embedded in Epon. Ultrathin sections (60–70 nm) of the blocks were then cut, stained with uranyl acetate and lead citrate, and viewed with a Hitachi H-600 electron microscope.

**Results**

**Endometrial changes**

Among the 50 mares examined, no EE lesions were observed in those up to 5 years of age (16 mares) (Table 1). Among the remaining 34 mares aged 6 years and older, EE lesions were observed in 30 (88.2%) (Table 1). In groups A, B and C, 5.9% (1/17), 75% (12/16) and 100% (17/17) of the mares, respectively, had EE lesions, suggesting that the incidence of EE tended to increase with advancing age (Table 1).

PF (Fig. 1), which increased in frequency with age, was differentiated into two types; one variant (Type A) was rich in periglandular stromal cells with large ovoid hyperchromatic nuclei and pale abundant cytoplasm, showing an acid mucopolysaccharide-positive matrix around the periglandular stromal cells (Fig. 2), while the other (Type B) was composed of periglandular stromal cells with spindle-
| Mare No. | Group | Age (years) | Parity | Estrous Cycle | Uterine Sites Examined |
|---------|-------|-------------|--------|---------------|-----------------------|
|         |       |             |        |               | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  |
| 1       | A     | 1           | 0      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 2       | A     | 1           | 0      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 3       | A     | 2           | 0      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 4       | A     | 2           | 0      | e             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 5       | A     | 2           | 0      | e             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 6       | A     | 2           | 0      | a             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 7       | A     | 3           | 0      | e             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 8       | A     | 3           | 0      | e             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 9       | A     | 3           | 0      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 10      | A     | 3           | 0      | a             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 11      | A     | 4           | 0      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 12      | A     | 4           | 0      | a             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 13      | A     | 4           | 0      | a             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 14      | A     | 5           | 0      | e             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 15      | A     | 5           | 1      | a             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 16      | A     | 5           | 2      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 17      | A     | 6           | 1      | a             | +  | +  | +  | +  | +  | +  | -  | +  |
| 18      | B     | 7           | 2      | e             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 19      | B     | 7           | 0      | d             | +  | +  | +  | +  | +  | +  | -  | +  |
| 20      | B     | 8           | 3      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 21      | B     | 8           | 5      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 22      | B     | 8           | 3      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 23      | B     | 8           | 4      | e             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 24      | B     | 10          | 5      | d             | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 25      | B     | 10          | 6      | a             | -  | +  | +  | +  | +  | +  | -  | +  |
| 26      | B     | 10          | 4      | d             | -  | +  | +  | +  | +  | +  | +  | +  |
| 27      | B     | 10          | 0      | a             | +  | +  | +  | +  | +  | +  | -  | +  |
| 28      | B     | 11          | 4      | d             | -  | -  | -  | -  | +  | +  | -  | -  |
| 29      | B     | 11          | 8      | d             | -  | -  | -  | -  | -  | -  | -  | -  |
| 30      | B     | 12          | 7      | d             | +  | +  | +  | +  | +  | +  | +  | +  |
| 31      | B     | 12          | 9      | e             | -  | +  | +  | +  | +  | +  | -  | +  |
| 32      | B     | 12          | 6      | a             | +  | +  | +  | +  | +  | +  | +  | +  |
| 33      | B     | 12          | 4      | d             | +  | +  | +  | +  | +  | +  | -  | +  |
| 34      | C     | 13          | 9      | a             | +  | +  | +  | +  | +  | +  | -  | +  |
| 35      | C     | 13          | 10     | a             | -  | +  | +  | +  | +  | +  | -  | +  |
| 36      | C     | 14          | 8      | e             | -  | -  | -  | -  | -  | -  | -  | -  |
| 37      | C     | 14          | 9      | a             | +  | +  | +  | +  | +  | +  | -  | +  |
| 38      | C     | 14          | 11     | a             | +  | +  | +  | +  | +  | +  | -  | +  |
| 39      | C     | 15          | 9      | d             | -  | -  | -  | -  | -  | -  | -  | -  |
| 40      | C     | 16          | 12     | e             | +  | +  | +  | +  | +  | +  | -  | +  |
| 41      | C     | 17          | 3      | e             | -  | -  | -  | -  | -  | -  | -  | -  |
| 42      | C     | 18          | 8      | d             | +  | +  | +  | +  | +  | +  | -  | +  |
| 43      | C     | 18          | 12     | a             | -  | +  | +  | +  | +  | +  | -  | +  |
| 44      | C     | 18          | 9      | b             | +  | +  | +  | +  | +  | +  | -  | +  |
| 45      | C     | 19          | 13     | e             | +  | +  | +  | +  | +  | +  | -  | +  |
| 46      | C     | 19          | 14     | d             | +  | +  | +  | +  | +  | +  | -  | +  |
| 47      | C     | 20          | 16     | u             | +  | +  | +  | +  | +  | +  | -  | +  |
| 48      | C     | 25          | 18     | u             | +  | +  | +  | +  | +  | +  | -  | +  |
| 49      | C     | 28          | 20     | u             | +  | +  | +  | +  | +  | +  | -  | +  |
| 50      | C     | 30          | 20     | d             | +  | +  | +  | +  | +  | +  | -  | +  |

A: group A, B; group B, C; group C, Parity; number of foalings, a: anestrus, d: diestrus, e: estrus, u: unknown.
Uterine sites: 1: right cranial horn, 2: mid-portion of the right uterine horn, 3: right caudal uterine horn, 4: left cranial horn, 5: mid-portion of the left uterine horn, 6: left caudal uterine horn, 7: uterine horn-body junction, 8: mid-portion of the uterine body, 9: area adjacent to the internal orifice. +: presence of endometrosis lesion, -: absence of endometrosis lesion. ○: presence of hemosiderosis, *: presence of endometrial cyst.
shaped, hyperchromatic nuclei and scanty and elongated cytoplasm (Fig. 3). The uterine gland epithelium of Type A showed disordered single or double layers of pleomorphic (irregular) epithelial cells, some of which were degenerative or necrotic, whereas that of Type B consisted of a single layer of uniform epithelial cells. In PAS-stained preparations, the basement membrane directly under the uterine glandular epithelium of Type A frequently showed swelling and partial tearing. In the glandular lumen in Type B PF, an eosin-stained inspissated secretion was occasionally observed.

SEF was characterized by fibroplasia and a decrease of uterine glands and small vessels, especially with advanced age. In particular, in the oldest mare, aged 30 years, complete fibrosis and loss of uterine glands and vessels were remarkable throughout the entire lamina propria, resulting in a marked thinning of this layer. The incidence of LL in the endometrium and vascular layer of the myometrium increased with advancing age.

Single or multiple ECs, generally showing a hemispherical shape, were observed protruding from the endometrium toward the uterine cavity and were diagnosed as lymphatic cysts arising from lymphangiectasia.

In the eight postpartum cases, ranging from 2–4 weeks postpartum, varying degrees of diffuse infiltration and accumulation of siderotic cells were observed in the upper lamina propria (Table 1).

Sclerotic changes in arteries within the entire uterine wall increased with advancing age. In the small arteries and arterioles, concentric and circumferential multiplication of elastic fibers mingled with collagen fibers was evident within all layers of the vessel wall (Fig. 4), with reduction of medial smooth muscle cells (Fig. 4). Ultrastructurally, the medial atrophy was characterized by irregular deformed smooth muscle cells showing undulations in their shape, degenerated smooth muscle cells and distension of the intercellular spaces, resulting in loss of anchoring junctions (cell adhesions) of smooth muscle cells (Figs. 5, 6). Calcification of the internal elastic lamina and arteriolar wall swelling with intra-parietal edematous vacuoles, fraying, disintegration and disruption of the swollen internal elastic were occasionally observed. In the terminal arterioles and capillaries, perivascular hyperplasia of the elastic fibers in the adventitia was evident. Hyperplasia of elastic fibers in the venous walls, venous luminal dilatation (phlebectasia) and adventitial perivascular elastosis in venules (phlebosclerosis) also increased with advancing age (Fig. 7).

There was also an age-related increase in the incidence of enlarged and tortuous lymphatic vessels (lymphangiectasia) with intramural hyperplasia of elastic fibers (Fig. 7). The dilated lymphatic vessels were filled with lymph. None of the vascular alterations described above were observed in the 14 maiden mares aged 1–5 years (No. 1–14; Table 1).

Relationships between the intrauterine distribution of EE and age

Among the 30 mares diagnosed as having EE, 14 (46.7%) were confirmed to have EE lesions at all 9 uterine sites examined; 0/17 (0%) mares in group A, 3/16 (18.7%) mares in group B, and 11/17 (64.7%) mares in group C had EE lesions at all 9 uterine sites (Table 1). The differences between the groups were significant (P<0.01), suggesting that the distribution of EE lesions increased with age.

Intrauterine distribution of ECs

ECs were observed in 12 of the 30 mares (40%) diagnosed as having EE lesions and in 10 of the 14 mares (71%) found to have EE lesions at all 9 uterine sites (Table 1). In 10 of the mares found to have ECs, ECs were observed at the junction of the right and left uterine horns and uterine body (Table 1).
**Alterations in the myometrium**

Mares aged over 10 years showed atrophy of smooth muscle fascicles in the myometrium, smooth muscle cell atrophy, fatty degeneration of atrophic myocytes and an increase in collagenous fibers mixed with elastic fibers in the spaces between smooth muscle bundles (Fig. 8). These changes increased both quantitatively and qualitatively with age. The degree and extent of the lesions appeared to be more severe in the outer longitudinal muscle layer than in the inner circular muscle layer.

**Discussion**

Aging is considered to be the most important factor related to the onset of EE [3, 6, 19]. In the 50 Thoroughbred mares evaluated in this study, EE was observed in those aged over 6 years, and the number of mares showing EE tended to increase with progressive age. EE was observed in all of the 21 mares aged over 12 years, thus suggesting that Japanese Thoroughbred mares aged 12 years and over are generally likely to have EE. In their evaluation of biopsied endometrium from Thoroughbred mares in the United Kingdom [19], Ricketts and Alonso observed EE in mares aged over 10 years but not in mares younger than 9 years. Similarly, Flores et al. observed EE in biopsied endometrium from Spanish mares aged over 15 years [3]; our present results confirm these previous findings.

Two types of PF were observed. Type A is considered to involve metabolically active stromal cells (ovoid-shaped, active fibroblasts), i.e., those actively synthesizing collagen with deposition of extracellular matrix and fibroplasias [6], whereas Type B is considered to involve metabolically inactive stromal cells (spindle-shaped, inactive fibroblasts), i.e., those in which collagen synthesis is arrested [6]. We speculate that Type A may be a lesion representing the early responsive stage of degenerative or necrotic epithelial cells of the uterine gland and that Type B may represent reparative changes in the glandular epithelium; that is, Type A may transform into Type B as EE progresses. We also postulate that the pleomorphic and degenerative epithelial cell morphology of the uterine gland epithelium in Type A is mainly attributable to damage of the basement membrane directly beneath the epithelial layer, with resulting active contacts between stromal cells and epithelial cells as well as interactions between the fibrotic extracellular matrix and glandular epithelial cells, ultimately leading to uterine glandular epithelial maldevelopment [6]. The Type B morphology may result from the stationary state of contact between epithelial and mesenchymal cells [6]. Although the cause of the basement membrane damage is unknown, it appears to be the main factor leading to PF, as this damage is known to cause alteration and deposition of extracellular matrix components around the basement membrane [6, 28]. Furthermore, PF has been implicated as a factor in the onset of early embryonic death, as it causes functional alterations of the glandular epithelia in fibrotic areas, particularly qualitative alterations of histotroph secretion by uterine gland epithelial cells [5, 13].

The present findings show that continuous insufficient lymphatic drainage may play an important role in the pathomorphogenesis of EE. Elastofibrosis in uterine wall arteries may be accompanied by elevated vascular resistance and reduced arterial function, thus leading to reduction of the endometrial arterial blood supply. Such arterial sclerosis may cause chronic venous congestion, thus leading to phlebosclerosis. Consequently, disturbances of lymphatic drainage (lymphatic stasis) may be induced, together with drainage disturbances caused by phlebosclerosis-induced reduction of endometrial venous blood flow. This vascular pathology may progress to disturbances in the lymphatic circulation, resulting in lymphatic edema. Subsequently, stromal edema may lead to so-called “edematous induction,” i.e., edema-induced fibroproliferation, of the endometrium (endometrial fibrosis). Comparison between Doppler ultrasonographic and histopathologic findings has revealed that elastofibrosis in vessels leads to reduced uterine perfusion [15].

The angiosclerotic changes observed in uterine wall arteries, veins and lymphatic vessels are identifiable as elastofibrosis, which was regarded as pathologic angiogenesis or angiopathy in previous studies [4, 21]. We observed that the vascular lesions first appeared in 6-year-old mares (Table 1; No. 17) as a mild pathologic change and then increased in both severity and incidence with age. Notably, modest angiosclerosis was observed in a nulliparous maiden mare aged 10 years (Table 1; No. 27), and we speculate that aging rather than parity plays an important role in the etiopathogenesis of angiosclerosis [4, 7, 21]. The efferent, concentric and multilayer distribution of elastic fibers is suggestive of a regenerative response of the injured elastic fibers [4, 17, 18]. Atrophy and loss of medial smooth muscle cells with aging may reduce the regenerative capacity of the cells, as it is known that these cells both break down and synthesize elastic fibers of the internal elastic lamina [8]. Regenerative hyperplasia of elastic fibers may remain in the tissue without being degraded completely, thus accumulating and further intensifying elastofibrosis or vascular lesions [18]. The appearance of angiosclerosis revealed by transmission electron microscopy in the present study was identical to that observed in previous studies [4, 18]. Although various authors have speculated that EE-affected vascular elastic fibers are degenerated [18], Grüninger et al. have demonstrated that accumulation of elastic fibers in angiosclerosis originates from not only degenerated but also
immature elastic fibers produced by “synthetic-type smooth muscle cells” [4].

The alterations in the intrauterine or endometrial arteries in the present study are pathomorphologically classified as elastosis or elastofibrosis [4, 18]. On the other hand, angiosclerosis in the extrauterine (uterine) artery during late pregnancy and the post-parturient period is known to consist of fibrosis or fibroelastosis, which may be caused by higher hemodynamic stress on the arterial wall [20, 25]. Although it remains unclear whether the pathogenesis of angiosclerosis can be considered identical between extrauterine and intrauterine vessels, we speculate that both hemodynamic and hormonal influences may cause elastosis or elastofibrosis in the intrauterine or endometrial vessels [4, 14].

In the 8 animals that were necropsied 2–4 weeks postpartum (No. 18, 23, 30, 32, 36, 39, 41, 43; Table 1), active phagocytosis of red blood cells and their metabolites by a large number of macrophages was observed in the superficial stratum compactum of the lamina propria. The present findings indicate that infiltration of siderotic cells into the endometrium occurs chronically and does not disappear rapidly postpartum; complete endometrial involution following parturition may not have occurred by the time of breeding during foal heat. This phenomenon may be one of the factors causing the conception rate after mating in the first postpartum heat to be lower in comparison with that during the next estrus [16].

We observed that the presence of EE in the endometrium at a single uterine site did not predict the presence of EE in all uterine sites in 4 mares less than 8 years of age (Table 1). However, in 14 of 27 mares (51.8%) aged 10 years and older, EE was observed at all 9 sites (Table 1). In 14 of 21 mares (66.7%) aged 12 years and older, EE was observed at all 9 sites (Table 1). This suggests that the age of the mare needs to be considered when diagnosing the presence of EE from a single-site endometrial biopsy sample.

The fact that ECs were observed in 40% of mares diagnosed as having EE, whereas no ECs were observed in mares without EE, suggests that the probability of EE being present may be approximately 40% if ECs are observed by ultrasonography or endoscopy. Because ECs were always observed at the uterine horn-uterine body junction, endometrial biopsy focusing on this site is recommended.

The significance of atrophy and loss of smooth muscle cells in the uterus with aging is unclear. Because poor myoelectrical tone in equine uteri with chronic infection has been implicated in the reduced function of uterine smooth muscle [23, 24], myometrial atrophy may be a factor that inhibits endometrial contractility during parturition and/or blastocyst implantation during the peri-implantation period.

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