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Is the pathological feature of necrotizing vasculitis isolated in the uterine cervix different from that of classic polyarteritis nodosa? A single institutional study

Kenji Yorita[1], Koki Hirano[2], Yuka Kai[2], Yu Tanaka[2], Yohei Takahashi[2], Kaoru Arii[3]

Abstract : Necrotizing vasculitis (NV), which could be observed in systemic necrotizing vasculitides such as classic polyarteritis nodosa, is characterized by fibrinoid necrosis, which typically involves the media. Among the gynecologic organs, the uterine cervix is the most frequent site of vasculitis; NV of the uterine cervix is usually asymptomatic and unrelated to systemic vasculitis. Pathological differences between isolated or single-organ NV and systemic necrotizing vasculitides have been rarely evaluated. Thus, this study aimed to determine the clinicopathological characteristics of NV of the uterine cervix and evaluate whether affected vessels are pathologically different from those in classic polyarteritis nodosa. We selected 405 cases of conization that were operated from 2003 to 2017 in our hospital, and follow-up data until 2018 was obtained for patients with vasculitis. NV was evaluated with sections stained by hematoxylin and eosin, elastica van Gieson, phosphotungstic acid-hematoxylin, and immunohistochemistry. Histological specimens of systemic necrotizing vasculitides were unavailable. NV and lymphocytic vasculitis (LV) of the uterine cervix were found in, respectively, six (1.5%) and 26 (6.4%) of the 405 cases; no granulomatous vasculitis was observed. All cases with vasculitis were asymptomatic and uneventful during the follow-up period, which suggested that the vasculitis of the uterine cervix in our study was single-organ vasculitis. Lymphocytes were the main inflammatory infiltrates in NV and LV, and neutrophilic infiltrate was inconspicuous. All NV cases showed subintimal localization of fibrinoid necrosis, which did not involve the media. The NV cases in our study differ from the typical NV in classic polyarteritis nodosa.

Keywords : necrotizing vasculitis, uterine cervix, isolated vasculitis, single-organ vasculitis, polyarteritis nodosa

Introduction

Vasculitis could be limited in a single organ. Such vasculitis is called isolated or localized vasculitis (1) and categorized as single-organ vasculitis according to the revised international Chapel Hill consensus conference in 2012 concerning the nomenclature of vasculitides (2). Among the gynecologic organs, the uterine cervix is the most frequent site of vasculitis. Histologically, vasculitis of the uterine cervix is usually non-granulomatous, which includes necrotizing vasculitis (NV) (3). Single-organ NV of the uterine cervix has been reported previously (3-16).

Single-organ NV has also been reported in various organs, such as skin (17), gallbladder (18), appendix (19), and testis (20). Single-organ NV is generally self-limiting and thus medication

[1]*Department of Diagnostic Pathology, Japanese Red Cross Kochi Hospital, Kochi-city, Kochi, Japan*
[2]*Department of Obstetrics and Gynecology, Japanese Red Cross Kochi Hospital, Kochi-city, Kochi, Japan*
[3]*Department of Internal Medicine, Japanese Red Cross Kochi Hospital, Kochi-city, Kochi, Japan*

Corresponding author: Kenji Yorita, MD, PhD
Department of Diagnostic Pathology, Japanese Red Cross Kochi Hospital, 1-4-73-11, Hadaminamimachi, Kochi-city, Kochi 780-8562, Japan
Tel: +81-88-822-1201, Fax: +81-88-822-1056, E-mail: kenjiyorita@gmail.com

not necessary, whereas systemic necrotizing vasculitides could be life-threatening and may require immunosuppressive therapy. However, pathological differences between single-organ NV and NV related to systemic vasculitis have been rarely evaluated and thus have not been fully understood. Only one relevant study was conducted (21). Hence, this study aimed to determine whether the pathological features of NV of the uterine cervix differ from those of classic PAN. Although the selected cases were the same with those used in our previous study (Int J Gynecol Pathol 39:379-383, 2020), the study aim and results of that study, which evaluated clinical significance of intracervical adipocytes, were quite different from the present aims and results.

Materials and Methods

We retrospectively selected 405 patients who received cervical conization between June 2003 and September 2017 in our hospital. Data obtained by loop electrosurgical excision procedure were not included in our study. Histological specimens of systemic necrotizing vasculitides were unavailable. The 405 cases and all conization specimens were included in a previous publication (Int J Gynecol Pathol 39:379-383, 2020). Each conization specimen was fixed with 10% formalin and was longitudinally cut into 12 sections. Subsequently, each cut section was paraffin-embedded, and all cut sections of each specimen were stained with hematoxylin and eosin. The pathological diagnoses of the conization specimens of the 405 cases were as follows: high-grade squamous intraepithelial lesion (HSIL, n=349), invasive squamous cell carcinoma (SCC, n=42), in situ and invasive adenocarcinoma (n=8), low-grade squamous intraepithelial lesion (n=2), chronic cervicitis (n=2), and endocervical glandular hyperplasia, not otherwise specified (n=2). Eight patients underwent second conization or hysterectomy with or without bilateral uterine adnexectomy. The uterine cervix of the eight patients after the second conization or hysterectomy was pathologically evaluated.

The types of inflammatory cells involved in vasculitis and the presence or absence of fibrinoid necrosis were recorded. NV was defined as vasculitis with fibrinoid necrosis. As described in a previous report (16), lymphocytic vasculitis (LV) was defined as vasculitis associated with predominantly lymphocytic infiltrate. Moreover, granulomatous vasculitis was defined as vasculitis with a granulomatous infiltrate. The following pathological parameters of vessels showing NV were evaluated: number and length of the minor axis, clockwise direction, and shortest distance from the mucosal surface to the superficial portion of the NV. The length was measured using FLOVEL Image Filing System (FLOVEL Inc., Tachikawa, Japan). Vessels showing NV were further evaluated using sections stained with elastica van Gieson (EVG), phosphotungstic acid-hematoxylin (PTAH), and Masson trichrome and sections immunostained with CD3 (clone F7.2.38, 1:200, DAKO, Glostrup, Denmark), CD4 (clone 1F6, 1:20, Novocastra Laboratories Ltd, Newcastle, UK), CD8 (clone 1A5, 1:160, Novocastra Laboratories Ltd, Newcastle, UK), CD79a (clone HM57, 1:200, DAKO, Glostrup, Denmark), CD20 (prediluted L26, DAKO, Glostrup, Denmark), and myeloperoxidase (clone 59A5, 1:80, Novocastra Laboratories Ltd, Newcastle, UK).

Clinical information, including age, body mass index (BMI; overweight 25≦BMI <30, obesity BMI≧30), gravidity, parity, hypertension, allergic state, autoimmune disease, serum surface antigen of hepatitis B virus (HBV), and antibody to hepatitis C virus (HCV), was obtained from medical records. Information on age at cervical conization was available in all 405 cases, and other clinical data were available in 214 cases only. Furthermore, data on medication, complete blood counts, and follow-up were obtained in patients with vasculitis in the uterine cervix. The follow-up period was from the date of cervical conization to September 2018.

The relationship of vasculitis and clinical factors was evaluated with Mann-Whitney U test, Fisher's exact test, or unpaired T-test. Statistical analysis

was performed with StatView 5.0 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $p<0.05$.

Comprehensive agreement for this study was obtained for all patients, and anonymized clinical information and pathological diagnosis were used in the analyses. This study was approved by the institutional review board of the Japanese Red Cross Kochi Hospital (No. 251).

Results

The age of the cases ranged from 22 to 80 years (mean ± standard deviation [SD], 41.6 ± 11.1 years). BMI ranged from 14.1 to 38.0 kg/m^2 (mean ± SD, 21.8 ± 3.5 kg/m^2). Gravidity ranged from 0 to 9 (mean ± SD, 2.1 ± 1.8), and parity from 0 to 5 (mean ± SD, 1.4 ± 1.2). Cervical conization was not performed during pregnancy or within 1 year after childbirth. Hypertension was observed in 18 cases, and allergic state, such as bronchial asthma, atopic dermatitis, allergic rhinitis, or food allergy, was noted in 48 cases. Nine patients had an autoimmune disease, including rheumatoid arthritis (RA, n=1), systemic lupus erythematosus (SLE, n=2), and Basedow disease (n=6). All patients were negative for serum surface antigen of HBV, whereas five patients were positive for anti-HCV antibodies.

NV, LV, and granulomatous vasculitis in the uterine cervix were found in six (1.5%), 20 (4.9%), and 0 (0%), respectively, of the 405 cases. Neither aneurysm nor infarction was observed. In patients with NV, HSIL (n=5) and adenocarcinoma in situ (n=1) were found in the uterine cervix. In patients with LV, HSIL (n=18) and SCC (n=2) were noted. Patients with NV or LV in the uterine cervix did not receive medical treatment or had autoimmune disease and hypertension. One of the patients with NV was positive for anti-HCV antibodies.

Clinical characteristics of the women with or without NV in the uterine cervix are shown in Table 1. Patients with NV or LV were not significantly associated with any clinical factors. All patients with NV or LV had normal complete blood counts, and eosinophilia was not observed. The follow-up period of women with NV and those with LV ranged from 13 to 96 months (mean ± SD, 50.8 ± 32.7 months) and 3 to 159 months (mean ± SD, 60.4 ± 46.9 months), respectively. All patients with NV or LV were alive and asymptomatic during the follow-up period, which suggested that systemic vasculitis and autoimmune diseases were unlikely. A detailed clinical evaluation was performed after conization in one patient with cervical NV; however, no systemic necrotizing vasculitides, such as classic PAN, antineutrophil cytoplasmic antibodies-related vasculitis, and autoimmune disease, were found.

Table 1. Clinical characteristics of women with or without necrotizing vasculitis in the uterine cervix

Valuables	Without NV	With NV	*p* value
Age	41.5±11.1	50.2±10.6	0.0544
Post-menopause	33	2	0.1260
Pre-menopause	177	2	
BMI	21.8±3.5	22.0±2.9	0.8673
Overweight	37/210	1/4	0.5453
Obesity	7/210	0/4	>0.9999
Parity	1.5±1.2	0.8±0.9	0.2438
Gravidity	2.1±1.8	1.0±1.4	0.2352
Hypertension	18/210	0/4	>0.9999
Allergy	47/210	1/4	>0.9999
HCV	4/210	1/4	0.0909

Age data were obtained from 405 cases (including six cases with NV), and data of other factors were from 214 cases (including four cases with NV). The calculated data related to age, BMI, parity, and gravidity are presented as mean values ± standard deviation and the other data as number.
NV, necrotizing vasculitis; BMI, body mass index; HCV, hepatitis C virus

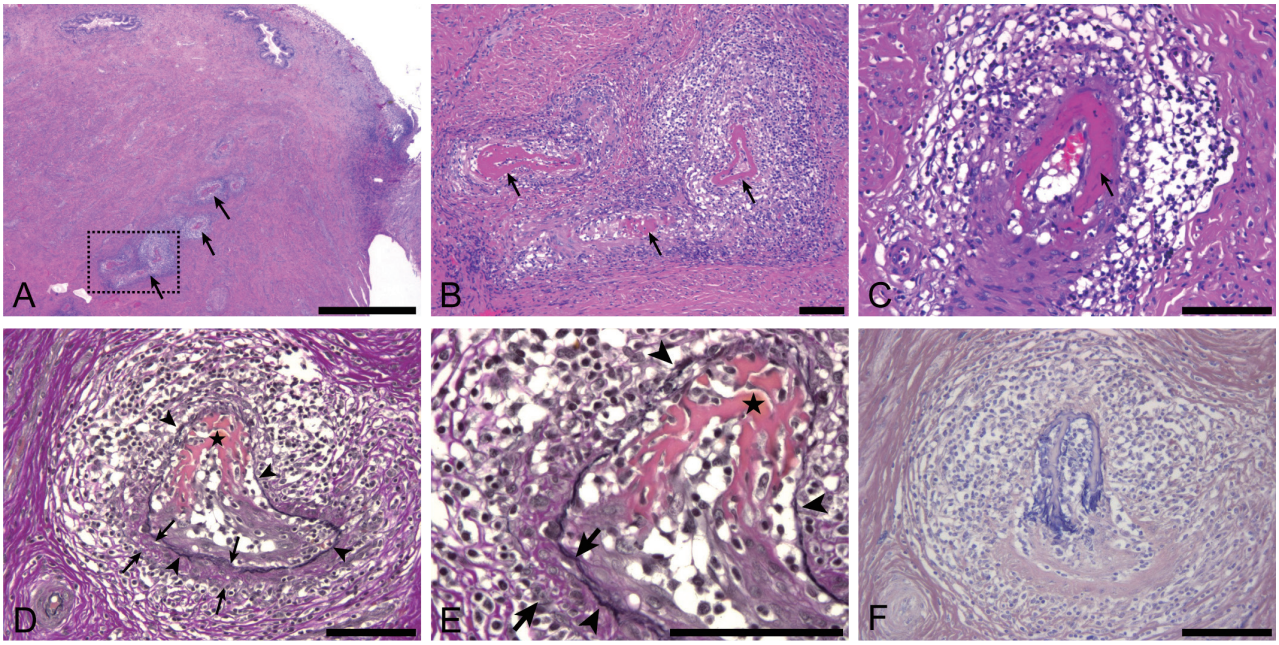

Figure 1. Necrotizing vasculitis of the uterine cervix.
A–C. Fibrinoid necrosis (arrows) is present in some vessels in the uterine cervix, where ulcer was not seen. B A higher magnification of the dotted square in A. Inflammatory cells, mainly lymphocytes, are involved and surround the affected vessels, which obscures the vascular wall. C. Fibrinoid necrosis in the wall of the muscular artery, which preserves the vascular lumen containing erythrocytes. D–E. An elastica van Gieson-stained section (E is a magnified image of D) showing that a vessel with necrotizing vasculitis has a largely preserved internal elastic lamina (arrowheads). Fibrinoid necrosis (red portions indicated by a star) is confined in the intimal or subintimal region, without extending to the media. The affected vessel shows obscure lumen and lacks the medial muscular coat (arrows) at the inflamed area. Polymorphonuclear leukocytes are hardly seen in E. F. A serial section of D, which was stained by phosphotungstic acid-hematoxylin, demonstrates that fibrin (blue) corresponds to fibrinoid necrosis of the affected vessel. Bars indicate 1 cm in A and 100 μm in B–F.

Thus, all cases with NV or LV suggested a single-organ vasculitis.

Uterine cervical NV of the six cases showed similar histological features, and the representative pathological features are shown in Figure 1A–E. NV showed segmental, focal, or circumferential involvement of the vascular wall. The affected vessels appeared to be mainly small-sized arteries or arterioles, although whether some of the involved vessels were arteries or veins could not be determined because of circumferential involvement. In all NV, fibrinoid necrosis was located at the subintimal (subendothelial) region based on HE- or EVG-stained sections without extending to the media (Figure 1C–E). The internal elastic lamina was largely preserved in all NV; however, the media and adventitia of the affected vessels were partly or circumferentially obscured by inflammatory cells, particularly lymphocytes (Figure 1C–E). In all NV, fibrinoid necrosis identified by hematoxylin and eosin-stained sections included fibrin with PTAH-stained sections (Figure 1F), and no fibrosis was observed with Masson trichrome-stained sections. Some NV preserved their vascular lumina (Figure 1C), and the other NV showed obscure lumina due to fibrinoid necrosis (Figure 1D, E). In all cases with NV, lymphocytes were predominantly noted in the vascular wall and surrounded the affected vessels. Plasma cells and macrophages were scattered, and eosinophils and neutrophils were few. Moreover, majority of the inflammatory cells involved in NV were CD3-positive lymphocytes. A mixture of CD4- or CD8-positive lymphocytes was also observed. CD79a/CD20-positive lymphocytes and myeloperoxidase-positive cells were scattered or hardly seen.

The number of NV ranged from 1 to 11, with a median (interquartile range, IQR) of 3.8 (1–5). Five of six NV cases (83%) showed NV located at 1, 11, or 12 o'clock positions. The vascular size of the vessels with NV ranged from 72 to 350 μm, with a median (IQR) length of 150 (119–287) μm, which is similar to that of LV (data not shown). Based on the Chapel Hill consensus conference (2), in our study, NV was found in small-sized vessels. In addition, the shortest distance from the mucosal surface to the superficial portion of NV ranged from 0.7 to 5.0 mm, with a median (IQR) distance of 2.0 (1.6–3.8) mm.

Of eight cases with additional resection after the first conization, four (50%) had NV in the additionally resected uterine cervix. The NV that was observed only in the uterine cervix was limited and adjacent to the ulcer region where the first conization was performed. In the eight cases, NV, LV, and granulomatous vasculitis were not found in the first conization specimen. Moreover, the four cases were uneventful during follow-up. In addition, all six cases with NV, which was detected in the first conization, had biopsy prior to cervical conization; however, the biopsied sites did not correspond to the sites of NV.

Discussion

In this study, we showed that single-organ, small-sized NV of the uterine cervix was incidentally found in 1.5% of conization specimen and that fibrinoid necrosis was present in the subintimal region, and did not extend to the media through the internal elastic lamina. The typical pathological features of NV in classic PAN include transmural necrotizing inflammation with destruction of the media with fibrinoid necrosis (22, 23). In our study, such effect of fibrinoid necrosis was not observed. Thus, in our study, fibrinoid necrosis might be called as subintimal hyaline deposition, which was based on a previous report (4). However, intimal or subintimal (subendothelial) localization of fibrinoid necrosis has been demonstrated in previous studies of NV (17, 21) and has been postulated as acute or subacute phase of cutaneous (single-organ) PAN (17).

Pathological diagnosis of small-sized NV isolated in the uterine cervix may need to rule out first the following: classic PAN; ANCA-associated vasculitis; infection, such as HBV-associated PAN; and monogenetic diseases, such as adenosine deaminase 2 deficiency (24). Among these diseases, classic PAN (25) and granulomatosis with polyangiitis (26) could involve the uterine cervix. A case of SLE or RA associated with NV of the uterine cervix has been reported previously(11, 27); thus, SLE and RA could also be included in the differential diagnoses. Moreover, HCV-associated cryoglobulinemic vasculitis may also be included in the differential diagnoses because it could also exhibit necrotizing vasculitis (28). In our cases with NV, these diagnoses were unlikely since all patients with NV showed no symptom at the diagnosis and during the follow-up period. Additional clinical examination may be unnecessary in the majority of cases with NV of the uterine cervix, as they have been often unrelated to systemic vasculitis (3, 10, 15, 16).

Whether pathological differences between NV isolated in the uterine cervix and NV of the uterine cervix related to systemic vasculitis exist remains to be established. As we could not find cases with NV of the uterine cervix related to systemic vasculitis, a relevant literature review was also conducted in this study. Mural localization of fibrinoid necrosis could be related to the pathological distinction between single-organ NV and NV related to systemic vasculitis. Matsumoto et al. (21) reported that fibrinoid necrosis is confined to the intima and inner media in isolated necrotizing arteritis of the uterus, gallbladder, pancreas, and spermatic cord, whereas in classic PAN, fibrinoid necrosis involved the intima and inner media to the outer media and adventitia. A previous study showed that subintimal localization of fibrinoid necrosis was most commonly found in cases with asymptomatic arteritis of the uterine cervix (4),

which is consistent with our findings. Francke et al. (9) reported fibrinoid necrosis involving the subintimal region and media in isolated necrotizing arteritis of the uterine cervix; however, they did not indicate whether fibrinoid necrosis involved the superficial or entire portion of the media. Aneurysm, which could be observed in classic PAN, in single-organ or isolated NV of the female genital tract has not been reported (4, 6, 11, 15, 21), which could mean that vascular destruction associated with NV has less damage in single-organ vasculitis than in classic PAN. Hence, superficial localization of fibrinoid necrosis in the vascular wall could be a sign of single-organ NV; however, this trend should be further examined in the uterine cervix because in cutaneous (single-organ) PAN, fibrinoid necrosis could extend outward to the media and adjacent areas through the destructed sites of the internal elastic lamina (17).

Moreover, we found that the predominant inflammatory cells involved in NV were T lymphocytes, which is consistent with the finding of previous studies that lymphocytes, primarily T lymphocytes, are the predominant inflammatory cells in isolated or single-organ NV involving the uterine cervix (4-13). Predominance of neutrophil in NV of the uterine cervix has not been reported based on our literature review. As the major inflammatory cells associated with NV in classic PAN are neutrophils (28, 29), the predominance of lymphocytic infiltrate in NV of the uterine cervix may suggest that such NV is isolated or single-organ vasculitis. However, inflammatory infiltrates in NV in classic PAN could also be predominantly chronic inflammatory cells (28, 29). In addition, Ganesan et al. (11) reported that in two cases of classic PAN, the predominant inflammatory cells involved in the NV of the uterine cervix are lymphocytes. Thus, the type of inflammatory cells could not predict isolated or systemic NV.

Furthermore, NV was observed in our cases that had additionally resected tissues; however, the vascular changes were possibly due to injury during the surgical procedure. Thus, NV should not be evaluated at the regions adjacent to the resected edges and previous biopsy sites. In this study, NV detected in the first conization specimen was not obtained from the previous biopsy site.

The pathogenesis of single-organ NV of the uterine cervix remains unknown. Nonetheless, as female predominance was confirmed in cases with isolated NV, female sex may be a risk factor (30). Hypertension, obesity, and drugs are also possible risk factors for single-organ NV involving the gynecologic organs (6, 9, 31). Moreover, NV of the uterine cervix was reported in patients with SLE (27), and HBV could be an etiology of classic PAN. However, these factors except for female sex were not observed in our study. In addition, HCV is also a probable etiology of cryoglobulinemic vasculitis, which could also exhibit NV (28). In our study, one patient with NV had HCV infection; however, cryoglobulinemic vasculitis was unlikely for the patient because of lack of symptoms, arthralgia, skin ulcers, and renal dysfunction. Mechanical injury during the surgical procedure, such as grasping with forceps, may result in NV; however, lymphocytic infiltrate in or around the involved vessels could not support the mechanical injury theory. Francke et al. (9) reported that immune-mediated inflammation is involved in the pathogenesis of isolated necrotizing arteritis of the female genital tract. In our cases, since all patients with NV have cervical neoplasia, cancer-related antigen-antibody complexes could not be excluded in the etiology of isolated vasculitis.

In conclusion, 1.5% and 4.9% of the 405 conization specimens had NV and LV, respectively. The vascular changes noted in our study were clinically insignificant because of uneventful follow-up; thus, the vascular changes were unrelated to systemic disease. Intimal or subintimal, not medial, localization of fibrinoid necrosis was observed in NV of the uterine cervix. Moreover, superficial localization of fibrinoid necrosis in the vascular wall might be a sign of single-organ NV of the uterine cervix; however, this hypothesis should be further evaluated.

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Conflicts of Interest and Source of Funding

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