

Leukocytoclastic Vasculitis Localized to the Uterine Cervix

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Abstract

Patients with gynecologic vasculitis should be evaluated for systemic disease as prognosis and treatment can vary depending on systemic involvement versus isolated disease. Leukocytoclastic vasculitis is a rare, immune-mediated small-vessel vasculitis. Leukocytoclastic vasculitis of the uterine cervix with systemic involvement has not previously been reported. A 25-year-old female with abnormal cervical cancer screening presented for colposcopy. Biopsies were notable for dysplasia and concurrent leukocytoclastic vasculitis. The patient later recalled a recurrent rash of her lower extremities, suspicious for systemic disease. Patients with gynecologic vasculitis should be evaluated for systemic involvement because prognosis and treatment differ from that of isolated disease. Additionally, leukocytoclastic vasculitis of the uterine cervix may be associated with both hormonal contraception and infections such as human papillomavirus, and any resulting cervical dysplasia should be monitored for progression and treated accordingly.

Keywords

vasculitis, leukocytoclastic, cervix, colposcopy

Abbreviations

CIN 1-3 = cervical intraepithelial neoplasia 1-3
GynV = gynecologic vasculitis
HPV = human papilloma virus
LCV = leukocytoclastic vasculitis
LGSIL = low grade squamous intraepithelial lesion
PAN = polyarteritis nodosa

Introduction

The term vasculitis refers to a heterogeneous group of conditions of vessel wall inflammation, which can be further differentiated by vessel size and histologic features. Leukocytoclastic vasculitis (LCV) is more specific, referring to a hypersensitivity vasculitis that is confined to small vessels and is characterized by neutrophilic inflammation in post-capillary venules.¹ Additional histopathologic features of LCV include endothelial swelling, fibrinoid necrosis, and erythrocyte extravasation. Leukocytoclastic vasculitis typically manifests with isolated cutaneous findings, usually as palpable purpura, macules, papules and/or bullae.² However, other organ systems may be involved, such as the kidneys, heart, gastrointestinal tract, lungs, and central nervous system. In some instances, LCV can be the predominant vasculitis seen in systemic diseases such as rheumatoid vasculitis and sarcoidosis.³ Triggers for LCV include infections, medications, vaccines, malignancies, and autoimmune diseases, but an estimated 50 percent of LCV cases are idiopathic.³⁻⁵ Prognosis is generally good and self-limiting, yet some studies have reported decreased overall survival rates in patients with LCV.³⁻⁵

Gynecologic vasculitis (GynV) refers to any inflammatory vascular condition within the female reproductive tract.⁶ Although rare, it has been well documented. GynV is typically an incidental finding on surgical specimens and most often confined to a single organ.^{6,7} Few cases of necrotizing vasculitis of the uterine cervix have been reported. More specifically, LCV of the uterine cervix has not been published in the medical literature.⁹ We present a case of LCV of the uterine cervix identified by colposcopic biopsy after abnormal cervical cancer screening in a patient with recurrent, self-limiting lower extremity skin changes.

Case

A 25-year-old nulliparous female presented to the gynecology clinic for colposcopy after cervical cancer screening resulted as a low grade squamous intraepithelial lesion (LGSIL). Human papilloma virus (HPV) testing was not completed. She was otherwise healthy and had no complaints. The patient was using an etonogestrel/ethinyl estradiol vaginal ring continuously for contraception.

The colposcopy was notable for a friable nulliparous cervix with abnormal contour. After application of acetic acid, acetowhite epithelium and punctation were noted at the 4, 8, and 11 o'clock positions with multiple small vessels visualized throughout the cervix. Biopsies at each location were taken, and endocervical curettage was performed.

The final pathology demonstrated cervical intraepithelial neoplasia grade 1 (CIN1) in all 3 cervical biopsy specimens along with microglandular hyperplasia consistent with exogenous hormone administration. Uniquely, each of the biopsies also showed atypical vascular changes characterized by fibrin thrombi, vessel wall destruction and cellular debris with many extravasated red blood cells (**Figure 1**), diagnostic for LCV. Endocervical curettage was negative for dysplasia and vasculitis.

The patient was referred to the rheumatology clinic for further evaluation. There, she revealed experiencing intermittent lower extremity skin changes, which were self-limiting and recurred sporadically. She was asymptomatic at the time of this clinical evaluation. Basic blood counts, metabolic panel, c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), hepatitis, human immunodeficiency virus (HIV), and autoimmune serologies such as antineutrophil cytoplasmic antibodies, antinuclear antibodies, anti-cyclic citrullinated peptide (CCP) antibodies, serum complements, rheumatoid factor, were then obtained and unremarkable. The patient was suspected to have

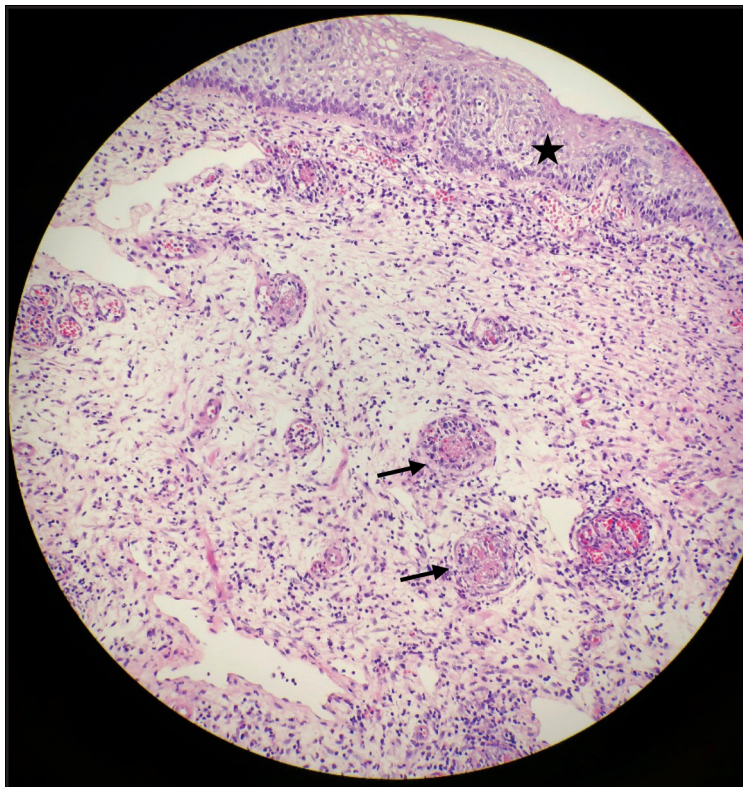


Figure 1. Initial colposcopy biopsy with fibrin thrombi, vessel wall destruction and neutrophilic cellular debris with many extravasated erythrocytes consistent with leukocytoclastic vasculitis (LCV, black arrows). Cervical intraepithelial neoplasia 1 (CIN1) shown (black star)

systemic LCV with skin and cervical manifestations. She was provided with a prednisone taper for future LCV skin recurrences and instructed to return to the gynecology clinic in 12 months to repeat the cervical cancer screening.

One year later, the patient's cervical Pap smear and HPV co-testing were significant for LGSIL and high-risk HPV positive status (HPV 16, 18, and 45 negative). The repeat colposcopy demonstrated acetowhite epithelium, punctation, and small vessels were again visualized at the 4, 8, and 11 o'clock positions; biopsies along with an endocervical curettage were obtained. The pathology was notable for CIN3 in the four o'clock specimen, and CIN1 was found within the 8 and 11 o'clock specimens and endocervical curettages. Additionally, LCV was again seen in the 11 o'clock specimen, and nonspecific vascular changes were present in the 4 and 8 o'clock specimens. The patient then underwent an uncomplicated loop electrosurgical excision procedure where high-grade cervical dysplasia and LCV were confirmed. The margins of the specimen were positive for high grade dysplasia and close observation was recommended. Throughout this time the patient denied further lower extremity skin lesions and had not used the prednisone taper. Prior to her next cervical cancer screening, the patient was lost to follow up after relocating out of the state.

Discussion

This case presents an opportunity to consider the evaluation of LCV and other GynV either found incidentally or in conjunction with systemic symptoms. This diagnosis presents important considerations including the etiology of the vasculitis, evaluation and treatment, and associated morbidity and mortality. Patients with GynV are most commonly asymptomatic; however, some may experience abnormal vaginal bleeding or present with pelvic masses.⁶ When diagnosed with LCV or other GynV, evaluation for systemic disease is recommended.^{3,6} A comprehensive work up includes erythrocyte sedimentation rate, complete blood count, basic metabolic panel, hepatitis panel, HIV testing, antistreptolysin titer, chest x-ray, antineutrophil cytoplasmic antibodies, antinuclear antibody, rheumatoid factor, serum complement, and serum or urine electrophoresis tests. If patient is not up to date, cervical cancer screening should be considered.^{4,6} Management includes removal of triggers such as the discontinuation of offending drug agents and treatment of diagnosed infections. Mild vasculitis cases are managed with supportive measures, but severe or chronic cases may require steroid administration.⁴

The prognosis of both LCV and other GynV is favorable. Naturally, as GynV is usually diagnosed after surgical resection of the affected organ, when confined to a single organ the GynV mortality rate is low.⁶ A 2016 retrospective analysis of 112 patients with LCV showed a 5-year survival rate of 75.6 percent, and of the 27 total deaths that occurred during the study period, only 2 were attributed to LCV. In this study, age over 65 years was associated with decreased survival.³ Another study of 84 patients reported a 5-year survival rate of 85 percent compared to 95 percent of the control population, with none of the 15 deaths directly related to LCV.⁵ In most cases, LCV is not the direct cause of mortality, instead it is an associated finding of infections, medications, and malignancies.

Overall, LCV is rare. A 2014 population study found an incidence rate of 0.0045 percent for biopsy-proven LCV.⁵ Vasculitis of any histology found within the female genital tract is also uncommon, with studies demonstrating an incidence of 0.04-0.15 percent of surgical specimens.^{6,7} In a case series, isolated necrotizing vasculitis similar to polyarteritis nodosa (PAN-type) was isolated from the uterine cervix in 66 percent of 88 cases reviewed.⁸ While small-vessel necrotizing GynV has previously been observed, this case is unique in that LCV of the uterine cervix has not been specifically documented.

In most LCV cases, the etiology is idiopathic. However, triggers for LCV are known and diverse. They include infections such as streptococcal upper respiratory tract infections, viral hepatitis, and mycobacteria.³⁻⁵ Regarding GynV, LCV may also be associated with sexually transmitted infections such as chlamydia, gonorrhea, HIV, syphilis, and HPV.⁴ The occurrence of GynV in the presence of HPV-related cervical dysplasia has previously been reported. One case reported chronic cervicitis as well as necrotizing granulomatous vasculitis after cervical conization.⁹ Sixteen cases of polyarteritis nodosa (PAN)-like necrotizing vasculitis were related to intraepithelial cervical neoplasia in another case series.¹⁰ Interestingly, all reported cases of vasculitis have been diagnosed on specimens obtained from cervical excisional procedures or hysterectomies and not simply colposcopic biopsies.⁷⁻¹² Although more research is needed, this may suggest an association between GynV, cervical dysplasia, and high-risk strains of HPV.

Other causes of LCV include drug reactions to many common medications including antibiotics, nonsteroidal anti-inflammatory drugs, antiepileptics, beta-blockers, immunosuppressants, diuretics, chemotherapy agents, diabetic medications, and antidepressants.³⁻⁵ Although the mechanism of action is unclear, a 2015 case report identified a patient with the diagnosis of cervical vasculitis onset approximately 5 weeks after medroxyprogesterone contraceptive injection suggesting progesterone immunomodulation as a trigger for the condition.¹³ This patient had been continuously using an etonogestrel/ethinyl estradiol vaginal ring for over 1 year suggesting possible progesterone-mediated vascular changes may be a factor in this case.

The occurrence of GynV with systemic involvement is less clear. One study looked to classify 163 patients with GynV, and of those 31 percent had systemic symptoms or signs of other organ system involvement. Systemic disease in these patients involved mostly musculoskeletal, pulmonary, or renal systems. Most patients complained of constitutional and musculoskeletal symptoms such as headache, polymyalgia rheumatica, and arthritis.

In conclusion, this case brings to light evidence that LCV can be found in the uterine cervix, and the importance of evaluating patient with isolated findings of LCV for systemic disease. The recommended workup is presented, as well as a review of causes, triggers, and prognosis. While many cases of LCV and other GynV are asymptomatic and self-limited, further evaluation should be considered, treatable conditions should be addressed, and patients monitored for the development of systemic disease. Although studies are limited, current evidence show decreased survivability in the setting of isolated and systemic LCV diagnosis, and patients should be aware of possible outcomes. Additionally, this case points to a possible correlation between both hormonal contraception and HPV infection with cervical LCV, although more research is needed to explore these associations.

The views expressed in this abstract/manuscript are those of the author(s) and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Conflict of Interest

None of the authors identify a conflict of interest.

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