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Incidental Isolated Vasculitis of the Uterine Cervix: Morphological Findings and Clinical Significance

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Gynecologic vasculitis has been reported as single-organ vasculitis and less frequently in the context of systemic vasculitis. The cause and pathogenesis of the isolated small vessel vasculitis of the uterine cervix, remain unknown. The purpose of this work is to research clinical, epidemiological, and morphological characteristics of isolated vasculitis of the cervix in long series of cases in order to make valid conclusions.

This is a case study of twelve patients with isolated small vessel vasculitis discovered incidentally in surgical specimens of the female genital tract. The latter are verified histologically, supported with immunohistochemistry, and studied in a retrospective analysis. The awareness of this rare type of cervical pathology is important for the daily diagnostical practice of the pathologist and the gynecologist, to exclude the further need of follow up or treatment.

Key words: vasculitis, cervix, uterus, conisation

Introduction

Systemic vasculitis is a group of heterogeneous conditions characterized by inflammation of the blood vessels, commonly affecting various vascular territories and organs [8]. Gynecologic vasculitis has been reported as single-organ vasculitis and less frequently in the context of systemic vasculitis. The significance of isolated vasculitis and whether isolated cases represent part of true systemic vasculitis, or a local inflammatory process is unclear, but in both cases the microscopical picture reveals PAN or PAN- like vascular lesions [12].

The cause and pathogenesis of the isolated small vessel vasculitis of the uterine cervix, remain unknown.

In this study we reviewed twelve cases of vasculitis of the uterine cervix diagnosed on pathology specimens in correlation with previous diagnostic and

surgical intervention, aiming to assess the significance of isolated vasculitis identified histopathologically in the gynecological tract.

Materials and methods

A retrospective study of twelve cases with isolated vasculitis involving the uterine cervix was performed at the Departments of Pathology, Jossigny Hospital, Jossigny, France and St. George University Hospital of Plovdiv, Plovdiv, Bulgaria for a 21-year period (2002–2022). Clinical and follow-up data were obtained from medical records and surgical pathology files. We inspect the clinical data for performed diagnostical and surgical interventions and history about autoimmune disorders and systemic vasculitis.

The study was approved by the local Ethics Committees of the hospitals. There is no patient – identifying information in any of the materials presented, and hence patient consent was not obtained.

All specimens were routinely fixed in 10% buffered formalin and embedded in paraffin for histological evaluation. Standard 4-μm-thick sections were cut from paraffin blocs.

Retrospectively, tissue sections from each case were observed independently by two pathologists. Sections were stained with haematoxylin-eosin (HE) and haematoxylin-eosin-saffron (HES).

The immunohistochemical study was performed using standard avidin-biotin peroxidase complex technique. The following primary antibodies (Dako, Caripenteria, California, USA, Leica Biosystems and Diagomics, France, Diagomics, France) were used: anti-CD3 (1:150, clone SP7); anti-CD 4 (1:50, clone RBT-CD4), anti-CD8 (1:100, clone SP16), anti-CD20 (1:100, clone L26); and anti-PD-L1 (1:200, clone QR1).

Results

Epidemiological, clinical and pathological data is summarized in **Table 1**.

In eleven of twelve cases, we found isolated, more or less, necrotizing small vessel vasculitis and in one we detected lymphocytic vasculitis (**Fig. 1A**).

All of the vascular findings were sustained with positive immunohistochemical markers CD3/C8, spotting the T-cell population in the lesions, while CD20, dentifying B-cells, is scantily positive (**Fig. 1B, 1C**).

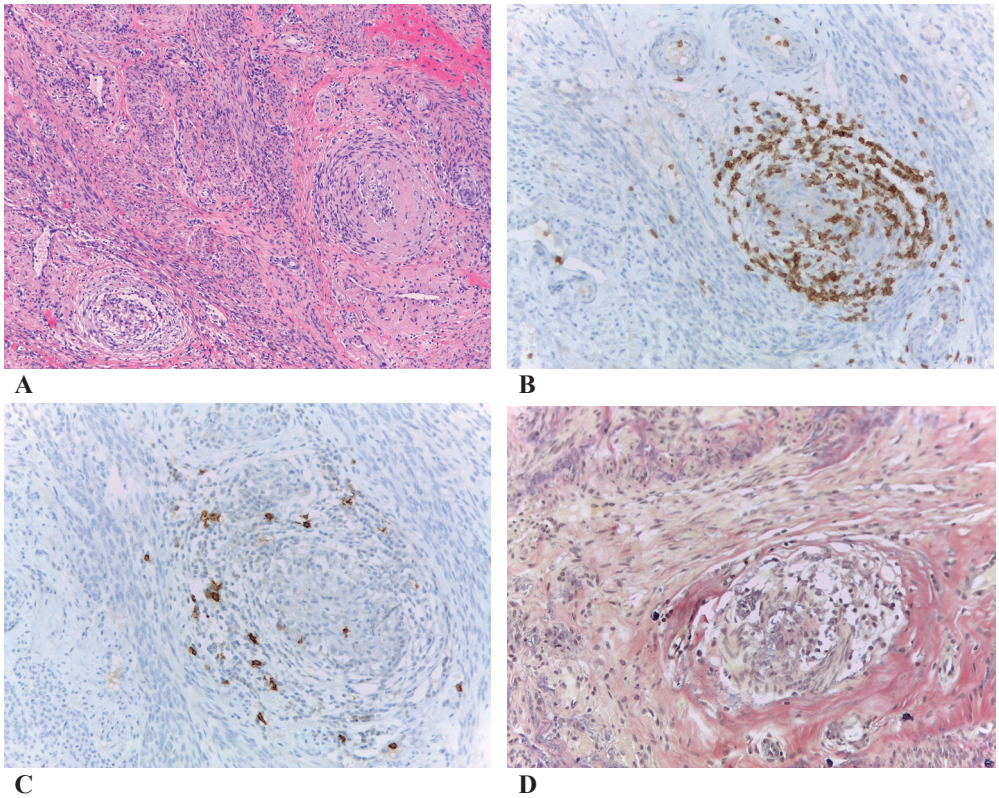
Staining with orcein showed thickening and focal dissociation of internal elastic membrane, which proof the arterial localisation of the lesion (**Fig. 1D**).

Other histological changes that we found in the cervix are resorptive inflammation with formation of foreign body granuloma in five of the patients (**Fig. 2A**), and stromal cervical fibrosis in the other seven (**Fig. 2B**). Absence of residual epithelial lesions were found in three of the speciments.

The age of the patients ranged from 28 to 82 years (mean age 45.5 years).

The main cervical pathology is the high-grade dysplastic changes of the epithelium, four cases with CIN III and one with carcinoma in situ. Once in a case we diagnosed CIN II, chronic cervicitis, isthmic cervical sclerosis and cervical polyp.

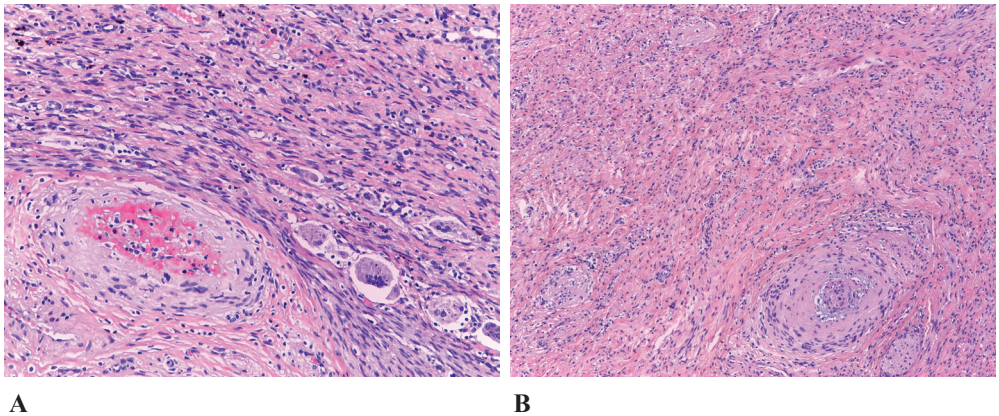
Eight of the cases have data for targeted diagnostical (smears, colposcopy-guided cervical biopsy) or surgical intervention (conisation) in the past months.



A **B**

C **D**

Fig. 1. Morphological and immunohistochemical characteristics of incidental isolated vasculitis of the uterine cervix. Necrotizing small vessel cervical vasculitis (right) or lymphocytic vasculitis (left) **(A)**. Immunohistochemically, transmuralniat inflammatory infiltrate rich of CD3+/ C8+ T-lymphocytes **(B)**, while CD20+ B – cells, is scantily positive **(C)**. There are thickening and focal dissociation of internal elastic membrane **(D)**. *Haematoxylin-eosin-saffron, × 100 (A); anti-CD3 and anti CD8, × 200 (B and C); elastica van Gieson staining, × 200 (D).*



A **B**

Fig. 2. Associated histological changes near to the incidental isolated vasculitis of the uterine cervix. Resorptive inflammation with formation of foreign body granuloma **(A)** and/or stromal fibrosis **(B)**. *Haematoxylin-eosin-saffron, × 200 (A) and × 100 (B).*

The mean time between the interventions and the apearance of the vasculitis is found to be 13,1 months.

Preoperative diagnosis and the main cervical pathology matched in the majority of the cases, in the others the previous diagnostical intervention had therapeutic outcome. After investigating the uterine corpus, we found adenomyosis in three, endometrial polyp in two and leyomyomas in one and absence of pathological changes in four of our cases.

No data for systemic vasculitis or other autoimmune diseases were found, exept one case with lymphocytic colitis without vasculitis.

Discussion

The clinical course of systemic PAN is mainly influenced by the involvement of circulation of brain, kidney or heart, whereas the severe prognosis of PAN results in acute cerebral hemorrhage or mostly in acute or chronic heart and renal failure. Treatment of choice is a combination of steroids and cyclophosphamide, but in cases of severe hemorrhage surgery is mandatory [10]. Isolated necrotizing arteritis of the PAN-type localized to the female genital tract is rare. In 1932, Plauth published the concept of isolated vasculitis of the uterine cervix [11]. Since then, 50 cases of isolated necrotizing vasculitis of the female genital tract have been reported [1,3,5,7,9,14,15,16].

Information about other etiological factors causing vasculitis of the female genital tract, like cytomegalovirus infection or secondary to local pressure exerted by a pessary, are found in the literature [2,4]. Drugs, applied during cone biopsy and used systemically may cause isolated vasculitis of the cervix [13,14].

Although it has been encountered as a self-limited lesion confined to a single organ, it can also be the first manifestation of systemic PAN, after which involvement of other organs is discovered. The lesions seen in isolated necrotizing arteritis are histologically indistinguishable from those of classic PAN, which are characterized by a segmental or circumferential fibrinoid necrosis with inflammatory infiltrate composed mainly of mononuclear cells [10], a finding that we report in our work. A study with 46 cases representing vasculitis affecting the female genital tract concluded that most of the cases appear to be examples of isolated vasculitis similar in histology and outcome to isolated arteritis at other sites [6]. It has been mentioned that foreign materials introduced by cone biopsies have been proposed to induce immune-complex mediated responses, with formation of foreign body reaction. They report 15 patients with a previous gynecological operations, but no comment about connection with developing of vascular lesions was made [6,11]. A clinicopathologic and immunohistochemical study of eleven cases of isolated necrotizing arteritis of the female genital tract report and support the relationship of the vascular lessions with hypersensitivity reaction to foreign materials after cone biopsy or a curettage [5].

We describe a series of cases of necrotizing vasculitis of the cervix. In all of the cases we found accompanying stromal changes: resorptive inflammation with formation of foreign body granuloma or stromal cervical fibrosis. In the majority of the cases we have data for previous surgical procedure. Our contribution to the literature about the etiology of isolated PAN-like cervical arteritis is the relationship between the vascular changes and previous surgical intervention, supporting the hypothesis for the role of hypersensitivity reaction caused by past procedures.

Our study enriches the literature with more information, relating the isolated necrotizing arteritis of the cervix caused by previous surgical or diagnostical intervention. The mean time between the interventions and the diagnosis of the vasculitis is found to be 13,1 months.

Diagnosis of true vasculitis is very important since true vasculitis requires systemic treatment. Presence of clinical data about previous diagnostical and theraptical gynecological operations on the cervix and absence of systemic vasculitis or other autoimmune diseases, exclude the further need of follow up or treatment.

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Table 1. Clinical details, pathological findings and follow-up (12 cases).

Number	Age	Previous surgical intervantions conisation,biopsy, ets. / months ago	Recent surgical intervantion	Preoperative diagnosis	Type of found vasculitis
1	53	conisation/18	total hysterectomy	Ca in situ	necrotizing vasculitis
2	45	cervical biopsy/12	total hysterectomy	adenomyosis, pelvix pain with metrorrhagia	necrotizing vasculitis
3	52	conisation/14	total hysterectomy	CIN II	necrotizing vasculitis
4	32	conisation/1	total hysterectomy	Ca in situ with microinvasion	necrotizing vasculitis
5	82	non	total hysterectomy	isthmic cervical sclerosis	necrotizing vasculitis
6	57	endometrial biopsy	cervical popypectomy	metrorrhagia postmenopausal	lymphocytic vasculitis
7	28	cervical biopsy/2,24,60	conisation	CIN III	necrotizing vasculitis
8	40	conisation/17	total hysterectomy	CIN I and AIS	necrotizing vasculitis
9	42	cervico-vaginal smears, vaginal biopsy/24,2	conisation	ASC-H,HSIL, VIN III	necrotizing vasculitis
10	40	cervical biopsy and conisation/2,60	conisation, cervical stenosis	ASC-H,HSIL, VIN III	necrotizing vasculitis
11	45	abortion, curretage/ 72	total hysterectomy	menometroragia, myoma utery	necrotizing vasculitis
12	30	conisation	total hysterectomy	invasive squamous cell carcinoma pT1b	necrotizing vasculitis

Number, number of cases; Age, age in years; CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma HSIL, high grade squamous intraepithelial lesion; VIN, vulvar intraepithelial neoplasia

IHC	Main cervical pathology	Additional cervical pathology	Pathological changes in the uterine corpus	History of diseaces with immune genesis
CD3+,CD8＋ CD20±	CIN III	stromal fibrosis	adenomyosis	non
CD3+,CD8＋ CD20±	chronical cervicitis	stromal fibrosis	adenomyosis	non
CD3+,CD8＋ CD20±	CIN II	resorptive inflamation with granuloma type foreign body	endometrial polyp	non
CD3+,CD8＋ CD20±	Ca in situ	resorptive inflamation with granuloma type foreign body	non	non
CD3+,CD8＋ CD20±	isthmical scrlerosis	inflamatory stromal fibrosis and hyalinosis	leiomyomas	microscopic colitis
CD3+,CD8＋ CD20±	cervical polyp	inflamatory stromal fibrosis	endometrial polyp	non
CD3+,CD8＋ CD20±	CIN III	inflamatory stromal fibrosis	non	non
CD3+,CD8＋ CD20±	no residual epithelial lesions	resorptive inflamation with granuloma type foreign body	endometrial polyp	non
CD3+,CD8＋ CD20±	CIN III	stromal fibrosis	non	non
CD3+,CD8＋ CD20±	CIN III	resorptive inflamation with granuloma type foreign body	non	non
CD3+,CD8＋ CD20±	non	stromal fibrosis	adenomyosis	non
CD3+,CD8＋ CD20±	no residual tumor lesions	resorptive inflamation with granuloma type foreign body and stromal fibrosis	non	non

in situ; ASC-H, atypical squamous cells, cannot rule out high grade squamous intra-epithelial lesion;