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Desquamative Inflammatory Vaginitis and Plasma Cell Vulvitis Represent a Spectrum of Hemorrhagic Vestibulovaginitis

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Objective: The aim of the study was to identify whether desquamative inflammatory vaginitis (DIV) and plasma cell vulvitis (PCV) are distinct clinicopathologic entities.

Materials and Methods: The pathology database identified biopsies described as "vaginitis" or "vulvitis" occurring in nonkeratinized epithelium or mucocutaneous junction. Exclusions were age less than 18 years, unavailable slides or records, concurrent neoplasia, or histopathology consistent with other entities. Clinical data included demographics, symptoms, examination, microbiology, treatment, and response. Histopathologic review documented site, epithelial thickness and characteristics, infiltrate, and vascular abnormalities. Cases were analyzed according to histopathologic impression of DIV or PCV based on previous pathologic descriptions.

Results: There were 36 specimens classified as DIV and 18 as PCV from 51 women with mean age of 51 years; 3 (6%) had concurrent biopsies with both. Pain was more common in PCV, but rates of discharge, itch, and bleeding were comparable. Rates of petechiae or erythema were similar and vaginal examination was abnormal in 72% of PCV cases. All DIV and 33% of PCV occurred in squamous mucosa; the remaining PCV cases were from mucocutaneous junction. Mean epithelial thickness, rete ridge appearance, exocytosis, and spongiosis were similar in DIV and PCV. Epithelial erosion, wide-diameter lesions, plasma cells, and stromal hemosiderin occurred in both but were more common in PCV. Lymphocyte-obscured basal layer, narrow-diameter lesions, hemorrhage, and vascular congestion were seen in both, but more common and marked in DIV.

Conclusions: Desquamative inflammatory vaginitis and PCV have overlapping symptoms, signs, and histopathologic features. They may represent a single condition of hemorrhagic vestibulovaginitis with varying manifestations according to location and severity.

Key Words: desquamative inflammatory vaginitis, papular colpitis, plasma cell vulvitis, plasma cell mucositis, vulva, vagina, histopathology, hemosiderin, lymphoplasmacytic, abnormal discharge

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D esquamative inflammatory vaginitis (DIV) is a poorly understood disorder that presents with abnormal discharge and vulvovaginal discomfort. Examination shows increased white-yellow discharge and vaginal erythema in a confluent or petechial pattern. Prevalence is uncertain as diagnosis may require access to specialized clinics but is estimated at 0.8%–4%.[1] Diagnosis involves point-of-care microscopy showing parabasal cells and more inflammatory than squamous cells, elevated pH, and purulent discharge not explained by other entities.[2] For clinicians without access to microscopy, Bradford and Fischer[1] describe a diagnostic approach using history, nonerosive vaginitis, negative microbiologic swab, and response to topical clindamycin or corticosteroids.[3] Several authors postulate that DIV is a reactive phenomenon—an inflammatory condition due to immune dysregulation, proposed to result from cross-reactivity between self-proteins and foreign antigens after exposure to infection, medication, systemic illness, or other triggers. This hypothesis is also expressed in reference to plasma cell vulvitis (PCV), balanitis, and gingivostomatitis.[3–6] Also called Zoon vulvitis, PCV presents with pain and well-demarcated shiny red-orange macules or patches at vulvar vestibule.[7,8] Similar to DIV, treatment usually involves topical corticosteroids and clindamycin.

At present, the main utility of biopsy in suspected PCV or DIV is to exclude erosive lichen planus (LP) or neoplasia, the former distinguished by basal layer degeneration or regeneration and the latter by basal layer atypia and immunohistochemical staining patterns.[3,9,10] Most DIV cases are easily distinguished clinically from LP and neoplasia, so biopsies are infrequent and highly selected; the result is scant literature on the histopathology of DIV. One series of 18 specimens showed focally dense lymphocytic infiltrate underlying thinned spongiotic epithelium with vascular congestion.[4] Multiple studies of PCV exist but are limited by several issues: (1) combination with or extrapolation from Zoon balanitis, (2) minimal data on PCV within a survey of vulvar dermatopathology, and/or (3) analysis focused on specific features like plasma cells, hemosiderin, or lozenge-shaped keratinocytes.[5,7,8,11–14] The synopsis of PCV histopathology is dense lymphoplasmacytic infiltrate underneath thinned spongiotic epithelium, accompanied by vascular congestion, hemorrhage, and/or hemosiderin. Given the similarities between DIV and PCV in presentation and histopathology, it is possible that they represent points on a disease spectrum in which similar etiologic events manifest differently according to anatomic site and severity.

The aim of the study is to determine whether DIV and PCV are distinct clinicopathologic entities through assessment of vulvovaginal specimens with epithelial abnormalities overlying stromal inflammation that do not fit into another diagnostic category.

METHODS

The Pathology North, Hunter New England database was searched for biopsies described as "vaginitis" or "vulvitis" submitted between April 2011 and February 2021. The Hunter New England Research Ethics and Governance Unit approved this retrospective histopathologic series (2020/ETH01880), and signed written consent was obtained for use of clinical photographs. Inclusion criteria were specimens from inner labia minora, vestibule, vagina, or cervix that contained mucocutaneous junction (MCJ) or

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nonkeratinized squamous epithelium with a clear histopathologic abnormality. Exclusion criteria were age less than 18 years, unavailable slides or records, concurrent vulvar neoplasia, or histopathology consistent with other entities to include lichen sclerosus (LS), LP, vestibulovaginal sclerosis, mycosis, and human papillomavirus (HPV)-related disease.

Review of hematoxylin and eosin (H&E)-stained slides yielded data on epithelial thickness measured at the thinnest site, surface features, glycogen status, exocytosis, spongiosis, and rete ridge pattern. Distribution of stromal infiltrate was described as unifocal, multifocal, or confluent and semiquantitatively characterized as scant, moderate, or marked. The interface between basal layer and infiltrate was evaluated as obscured or nonobscured. Lesion size was assessed by measuring the width and deepest extent of the largest focal infiltrate. When the infiltrate was uniform, biopsy width was recorded. Cell types were recorded in descending frequency.

Vascular alterations were divided into congestion, hemorrhage, or hemosiderin, noted as epithelial and/or stromal. Hemorrhage quantity was recorded with descriptive terms: "sprinkles" referred to scattered erythrocytes, "speckles" to multiple small clusters, "clumps" to midsize groupings, and "blobs" to semiconfluent hemorrhage. Perls stain was obtained when hemosiderin was suspected but not obvious on H&E. After blinded review, the pathologist (J.S.) provided an impression of DIV or PCV, based on previous studies. When

TABLE 1. Clinical Features of the Women With Histopathologic Diagnosis of DIV and PCV

	All cases (N = 51)	DIV (n = 33)	PCV (n = 18)	p
Age, mean (range), y	51 (21–74)	50 (21–70)	57 (31–74)	.06
Seen by vulvar specialist, n (%)	21 (41)	7 (21)	14 (78)	<.001[a]
Postmenopausal, n (%)	34 (67)	20 (61)	14 (78)	.35
No estrogen	15 (29)	10 (30)	5 (28)	.35
Topical estrogen	7 (14)	4 (13)	3 (17)	.69
Systemic replacement	12 (24)	6 (18)	6 (33)	.3
Previous hysterectomy, n (%)	11 (22)	10 (30)	1 (6)	.07
Immune dysfunction, n (%)	15 (29)	10 (30)	5 (28)	1
Symptoms, n (%)[b]				
Pain or dyspareunia	31 (61)	16 (38)	15 (83)	.02[a]
Abnormal discharge	29 (57)	17 (51)	12 (67)	.38
Itch	9 (18)	7 (21)	2 (11)	.46
Abnormal bleeding	8 (16)	6 (18)	2 (11)	.7
No symptoms elicited	5 (10)	5 (15)	0	.15
Examination, n (%)[b]				
Erythema	31 (61)	19 (58)	12 (67)	.56
Petechiae	20 (39)	12 (36)	8 (44)	.76
Abnormal discharge	11 (22)	7 (21)	4 (22)	1
Normal or other	9 (18)	9 (27)	0	.02[a]
Biopsies taken per patient, n (%)				
1	29 (57)	19 (58)	10 (56)	1
2	11 (22)	7 (21)	4 (22)	1
≥3	10 (20)	7 (21)	3 (22)	1
Identified trigger, n (%)	16 (31)	11 (33)	5 (28)	.77
Clinical impression, n (%)				
DIV	22 (43)	15 (45)	7 (33)	.77
PCV	5 (10)	0	5 (28)	.004[a]
Erosive LP	7 (21)	4 (12)	3 (17)	.7
Not recorded or other	17 (33)	14 (42)	3 (17)	.07
Microbiologic or nucleic acid results, n (%)				
Normal flora	34 (67)	22 (67)	12 (67)	1
Candida species	3 (6)	1 (3)	2 (11)	.28
Other	3 (6)	2 (6)	1 (5)	1
Not performed	11 (21)	8 (24)	3 (17)	.73
No treatment provided	7 (14)	7 (21)	0	.04[a]
Outcome if treated, n (%)				
No change or minimal improvement	4/44 (9)	3/26 (12)	1 (6)	.63
Improved	16/44 (36)	10/26 (38)	6 (33)	.76
Resolved	19/44 (43)	9/26 (35)	10 (55)	.22
Lost to follow-up	5/44 (11)	4/26 (15)	1 (6)	.63
Follow-up, mean (range), mo	17 (1–96)	15 (1–60)	21 (2–96)	.46

[a] Indicates value <0.05.

[b] Women could have more than 1 symptom, examination finding, and treatment.
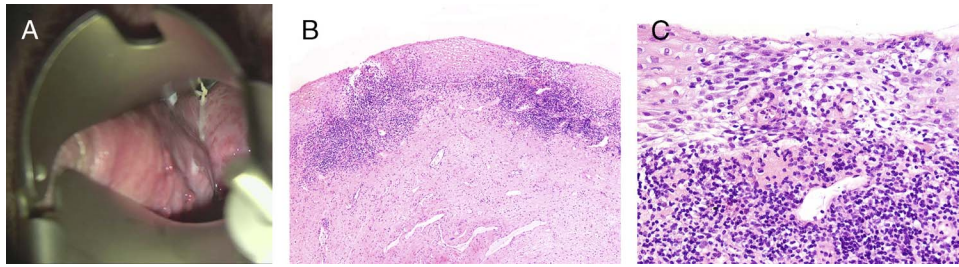
FIGURE 1. A, A 61-year-old patient with vulvovaginal pain, abnormal discharge, pink-red macules at lateral fornix and cervix, and improvement on high-potency topical steroids and vaginal clindamycin, consistent with DIV; B, DIV: 2 foci of thinned vaginal epithelium overlying nonconfluent dense infiltrate containing hemorrhage, H&E ×40. C, Thinned spongiotic epithelium with focal hemorrhage, obscured basal layer, and dense lymphoplasmacytic infiltrate with vascular congestion; absent hemosiderin confirmed by negative Perls stain (not shown), H&E ×200.

multiple biopsies from a single patient and site showed similar histology, data were collected from the most representative specimen.

Demographic data included age, estrogen status, body mass index (BMI), hysterectomy, tobacco use, and immune dysfunction defined as autoimmune disease or immunosuppressive medications. Clinical information included symptoms, historic triggers, examination, microbiology, impression, initial treatment and response, subsequent treatment, and duration of follow-up. None of the submitting clinicians performed wet mount. Descriptive statistics were performed, categorical data were compared with Fisher exact test, and means were compared with the Student t test.

RESULTS

There were 54 specimens from 51 women with a mean age of 51 years (21–74 y). Three patients had concurrent PCV on vulvar and DIV on vaginal biopsies and were assigned to PCV for clinical analysis. There were no differences between PCV and DIV in age, estrogen status, hysterectomy, or immune dysfunction (see Table 1). The latter comprised 5 (33%) with thyroid disease, 2 (13%) on systemic corticosteroids, 1 (7%) undergoing chemoradiation for cervix cancer, and 1 each with ulcerative colitis, common variable immunodeficiency, systemic lupus erythematosus, Behcet disease, Raynaud disease, disseminated sarcoidosis, and undifferentiated connective tissue disorder. Diabetes mellitus was present in 1 case of DIV. Data were available on tobacco in 43 of 51 (84%) and BMI in 29 of 51 (57%); among these, 7 of 43 (16%) were smokers and 7 of 29 (24%) had BMI greater than 30 kg/m^2, with no difference between groups. There were 4 cases of comorbid LS (8%), all separate to biopsy sites and managed with topical corticosteroids.

Clinicians did not elicit symptoms in 5 DIV cases (15%), of whom 1 attended for LS surveillance and 4 for colposcopy. Desquamative inflammatory vaginitis and PCV had similar rates of discharge, itch, and abnormal bleeding, but pain was more common in PCV (15 of 18 [83%] vs 16 of 33 [38%], $p = .02$). Four DIV cases (12%) reported neither abnormal discharge nor pain; 3 had abnormal bleeding and 1 had itch. Historical triggers were identified in 16 (31%) and included illness/injury in 5 (31%), surgery in 5, antibiotics in 3 (19%), vulvovaginal medications in 2 (13%), and travel in 1 (6%). Petechiae, erythema, and abnormal discharge were similar in DIV and PCV (see Figures 1, 2), but nonspecific descriptions were more common in DIV, to include scattered acetowhite change or poor Lugol uptake in 5 (15%), "inflamed cervix" in 1, vaginal polyp in 1, papillary vaginal mucosa in 1, and normal in 1. Among DIV cases, clinicians documented vulvar erythema in 7 (21%), further specified as vestibular red lesions in 3 (10%). Descriptors of vulvar examination in PCV included erythematous lesion(s) in 7 (39%), "appearance of Zoon's" in 4 (22%), not specified in 4 (22%), and "introital petechiae" in 3 (17%). Speculum examination was abnormal in 13 PCV cases (72%), showing vaginal petechiae in 7 (54%) and diffuse erythema in 6 (46%). There was atrophy in 3 of 18 (17%), and vagina was not inspected in 2 (11%).

Vaginal microbiology was obtained in 79%, nucleic acid testing for chlamydia, ureaplasma, mycoplasma and/or trichomonas in 20%, and cervical screening in 39%. *Gardnerella vaginalis* was identified in 1 DIV case and ureaplasma in 1 PCV and 1 DIV case. Biopsies occurred in the operating room in 1 PCV and 9 DIV cases; indications were intolerance of office assessment in 6 (12%) and concurrent surgery in 4 (8%) to include hysterectomy, bilateral salpingo-oophorectomy, hysteroscopy, and distal urethral resection. Colposcopy occurred in 1 PCV and 7 DIV cases for non-16/18 HPV in 4 (8%), HPV 16 and HPV 18 in 1 each, and negative HPV with atypical glandular cells in 1 and high-grade squamous intraepithelial lesion in 1. Clinical impression was documented in 47 of 51 (92%) and matched pathology results 23 of 47 (49%), with an additional 4 PCV cases (9%) identified as DIV. The most common nonconcordant diagnosis
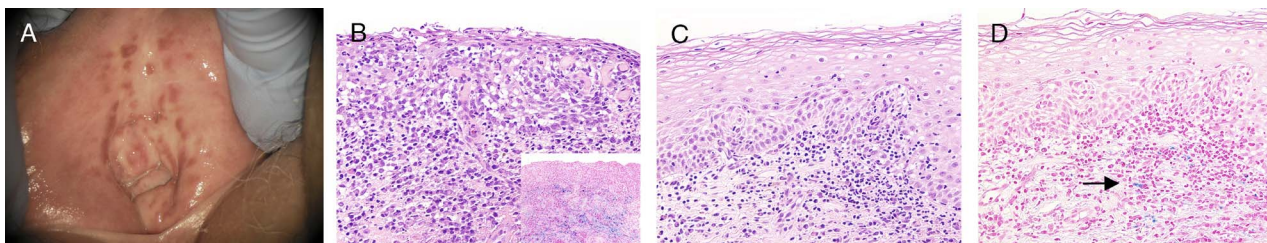
FIGURE 2. A, A 74-year-old patient with vestibular and vaginal orange-red macules and abnormal discharge. B, PCV: vestibular epithelium with intracytoplasmic vacuoles, extravasated lymphocytes and neutrophils, and unobscured reactive basal layer; stroma shows vascular congestion, plentiful hemosiderin, and dense confluent infiltrate of plasma cells and lymphocytes, H&E ×200; inset of vestibular Perls shows diffuse hemosiderin, ×100. C, DIV: vaginal epithelium with spongiosis and exocytosis overlying papillary lymphoplasmacytic infiltrate focally obscuring the basal layer and accompanied by sporadic hemosiderin, H&E ×200. D, DIV: vaginal Perls shows confluent moderate infiltrate and occasional hemosiderin (arrow), ×200.

was LP in 7 (21%). In DIV, other presumptive diagnoses were prolapse or polyp in 3 (6%) and 1 each with LS, cutaneous sarcoidosis, postradiation change, vulvodynia, candidiasis, and trichomonas. In PCV, other nonconcordant impressions were estrogen deficiency in 2 (11%) and LS in 1 (6%).

Treatment was more commonly prescribed at the initial visit in PCV compared with DIV (18 of 18 [100%] vs 26 of 33 [79%], $p = .04$). All cases of DIV diagnosed by a vulvar specialist received treatment. Topical corticosteroids were sole therapy in 9 DIV cases (27%) and combined with clindamycin in 8 (24%).

TABLE 2. Histologic Features of DIV and PCV

	Total (*N* = 54)	DIV (*n* = 36)	PCV (*n* = 18)	*p*
Biopsy site, *n* (%)				
Nonkeratinized epithelium	42 (78)	36 (100)	6 (33)	<.001[a]
Mucocutaneous junction	12 (22)	0	12 (67)	<.001[a]
Epithelial thickness; mean (range), mm	0.08 (0.02–0.3)	0.08 (0.02–0.3)	0.07 (0.02–0.18)	.2
Distribution of abnormality, *n* (%)				
Single	4 (7)	4 (11)	0	.29
Multiple foci	29 (54)	25 (70)	4 (22)	.001[a]
Confluent	21 (39)	7 (19)	14 (78)	<.001[a]
Width of largest abnormal focus, mean; SD (range), mm	1.5 (0.2–8)	1.3; 1 (0.2–5)	2.7; 1.8 (0.6–8)	<.001[a]
Depth of largest abnormal focus, mean (range), mm	0.51 (0.1–1.5)	0.5 (0.1–1.5)	0.6 (0.2–1.5)	.28
Epithelial surface, *n* (%)[a]				
Normal	23 (42)	19 (53)	4 (22)	.04[a]
Eroded	28 (52)	17 (47)	11 (61)	.4
Parakeratosis	3 (6)	0	3 (17)	.03[a]
Glycogen status, *n* (%)				
Normal	39 (72)	26 (72)	13 (72)	1
Reduced or absent	15 (28)	10 (28)	5 (28)	1
Rete ridges, *n* (%)				
Normal	36 (67)	25 (69)	11 (61)	.56
Reduced	16 (29)	11 (31)	5 (28)	1
Elongated	2 (4)	0	2 (11)	.11
Obscured basal layer, *n* (%)	32 (59)	28 (78)	4 (22)	<.001[a]
Exocytosis, *n* (%)	53 (98)	36 (100)	17 (94)	.33
Spongiosis, *n* (%)	43 (80)	28 (78)	15 (83)	.73
Hemosiderin, *n* (%)	22 (41)	7 (19)	15 (83)	<.001[a]
Epithelial hemorrhage, *n* (%)				
Nil	22 (41)	12 (33)	10 (55)	.15
Sprinkles	7 (13)	3 (8)	4 (22)	.21
Speckles	13 (24)	10 (28)	3 (17)	.51
Clumps and blobs	12 (22)	11 (31)	1 (6)	.04[a]
Stromal hemorrhage, *n* (%)				
Nil	18 (33)	9 (25)	9 (50)	.12
Sprinkles	10 (19)	4 (11)	6 (33)	.07
Speckles	13 (24)	11 (30)	2 (11)	.18
Clumps and blobs	13 (24)	12 (34)	1 (6)	.04[a]
Vascular congestion present, *n* (%)	23 (43)	18 (50)	5 (28)	.15
Stromal infiltrate, *n* (%)				
Scant	6 (11)	6 (17)	0	.16
Moderate	20 (37)	12 (33)	8 (44)	.55
Marked	28 (52)	18 (50)	10 (56)	.78
Predominant infiltrate cell type, *n* (%)				
Lymphocytes	46 (85)	36 (100)	10 (56)	<.001[a]
Plasma cells	8 (15)	0	8 (44)	<.001[a]
Secondary infiltrate cell type, *n* (%)				
Nil	14 (26)	14 (39)	0	.002[a]
Lymphocytes	7 (13)	0	7 (39)	<.001[a]
Plasma cells	29 (54)	20 (55)	9 (50)	.78
Neutrophils	4 (7)	2 (6)	2 (11)	.59

[a] Indicates *p* < .05.

Other treatments included neuromodulators in 5 (15%), topical clindamycin in 4 (12%), topical estrogen in 3 (9%), antifungals in 3, oral antibiotics in 1, and intradermal steroid injection in 1. In 6 DIV cases (18%) not improved with initial management, topical steroids or clindamycin was subsequently instituted. Maintenance regimens were prescribed in 11 DIV cases (33%), with 5 on combined clindamycin and steroid and 3 each on the respective single agent. Initial PCV therapy was topical steroid alone in 8 (44%) and combined with clindamycin in 7 (39%); 3 (17%) had single-agent clindamycin. A steroid maintenance regimen was instituted in 13 PCV cases (72%) and 1 had treatment of a single recurrence; the remainder resolved or did not follow up. Suppressive therapy was more common in PCV than DIV (13 of 18 [72%] vs 11 of 33 [33%], $p = .01$). Adjunctive vaginal estrogen was provided in 3 cases each of DIV and PCV.

All DIV and 33% of PCV cases occurred in squamous mucosa (see Table 2). The remaining PCV cases occurred in vestibular epithelium with parakeratosis, representing MCJ.[15] Clinicians obtained biopsies from vagina in 33 of 36 (92%), cervix in 2 (6%), and vestibule in 1 (3%) among cases of histologic DIV. Biopsies identified as PCV were collected from vestibule in 17 (94%) and vagina in 1 (6%). Epithelial thickness, glycogen status, rete ridges, exocytosis, and spongiosis were similar. Focal erosion occurred in both, but DIV was more likely than PCV to have a normal surface (19 of 36 [53%] vs 4 of 18 [22%], $p = .04$).

Lesion size was wider in PCV than DIV, whereas lesion depth was similar (see Table 2). Most DIV cases showed unifocal or multifocal lesions with epicenters at papillary processes; in 29 of 36 (81%), the largest focus measured less than 2 mm. The usual appearance of DIV was thinned spongiotic epithelium overlying lymphocytic infiltrate with localized hemorrhage and vascular congestion (see Figure 1). Most PCV cases were wide lesions containing focally eroded spongiotic epithelium overlying a band-like lymphoplasmacytic infiltrate with scattered hemosiderin and lesion width 2 mm or greater in 13 of 18 (72%; see Figure 2). However, DIV sometimes displayed a confluent infiltrate, hemosiderin, and/or absent hemorrhage, whereas PCV could have focal infiltrates, hemorrhage, and/or absent hemosiderin (see Figures 2, 3). The infiltrate was moderate or marked in all PCV cases, whereas in DIV it ranged from scant to dense (see Figure 4).

The interface between basal layer and infiltrate was more often obscured by lymphocytes in DIV than PCV (28 of 36 [78%] vs 4 of 18 [22%], $p < .04$; see Table 2; Figures 1, 2). Plasma cells were predominant in 8 of 18 PCV (44%), whereas all DIV cases were lymphocyte predominant. Eosinophils were present in 6 cases. Hemorrhage occurred across epithelium and stroma in both but in DIV was more often seen in clumps and blobs while in PCV as sprinkles or speckles [12 of 36 (34%) vs 1 of 18 (17%), $p = .04$]. Vascular congestion and hemosiderin also occurred in both, but hemosiderin was more frequent and denser in PCV than DIV (15 of 18 [83%] vs 7 of 36 [19%], $p < .001$; see Figures 2, 3). There was 1 PCV case without congestion, hemorrhage, or hemosiderin; all other specimens showed at least 1 vascular abnormality.

DISCUSSION

There is no single clinicopathologic feature that discriminates between DIV and PCV. Both occur in reproductive-age and postmenopausal patients with similar rates of historical triggers and immune dysfunction. They demonstrate overlapping symptoms of pain, discharge, itch, and bleeding. Examination shows erythema and/or petechiae, and greater than 70% of PCV cases have vaginal findings suspicious for DIV. Most PCV and DIV cases improve with topical corticosteroids and/or clindamycin. In both, the basal layer may be obscured or unobscured by lymphocytes, epithelial hemorrhage ranges from absent to plentiful, and spongiosis and exocytosis are common but not universal. Both show a variable ratio of lymphocytes to plasma cells and have any combination and degree of vascular congestion, hemorrhage, and hemosiderin. As in any biologic phenomenon, some cases contain mixed features and do not fit easily into categories comprising each end of the spectrum. Overlap across multiple features supports the concept that DIV and PCV encompass a clinicopathologic spectrum with variation driven by severity and site. An alternate explanation is that PCV and DIV represent one among several stereotypical vulvovaginal reaction patterns, alongside lichenoid, granulomatous, and acantholytic. An expanding clinicopathologic knowledge base permits improved differentiation between previously amalgamated diagnoses, like erosive LP and DIV, even if their etiologic mechanisms remain a mystery.[16]

The 3 cases of concurrent histologic PCV and DIV strengthen the hypothesis that these are same condition manifesting differently at vulvar and vaginal sites. Several case reports apply labels of "plasma cell vulvovaginitis" or "plasma cell vaginitis and cervicitis" to cases of red macules extending across vestibule and vagina with biopsies showing dense lymphoplasmacytic infiltrate with hemorrhage or hemosiderin.[17–20] Among 18 patients with DIV in the series by van der Meijden and Ewing,[4] 6 (33%) had simultaneous vulvar biopsies suggestive of PCV. Their discussion identified that PCV is too rare an entity to occur so often by chance alongside DIV and likewise postulated that they are the same reactive process variably expressed across the lower genital tract. If biopsy location is not considered, a histologic characteristic that drove case definition was lesion width—narrow in DIV and wide in PCV. Many biopsies categorized as DIV in this study resemble description of DIV by van der Meijden and Ewing[4] as "focal aggregate lymphocytes measuring 1 mm in diameter under thinned epithelium…[with] mild polymorphic infiltrate in epithelium
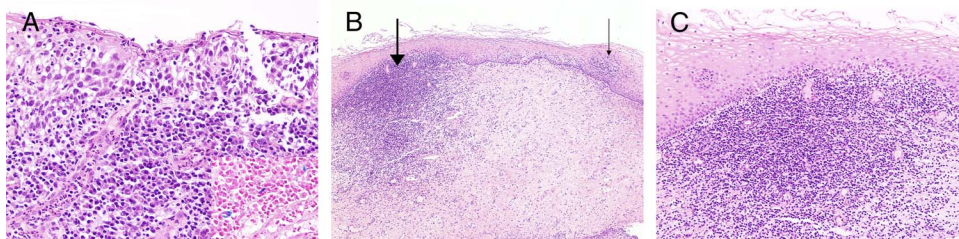
FIGURE 3. A 58-year-old patient with concurrent PCV and DIV; A, PCV: vestibular nonkeratinized epithelium containing neutrophils and eosinophils, spongiosis, intracytoplasmic vacuoles, and unobscured basal layer; stroma shows dense confluent infiltrate of plasma cells, lymphocytes, and rare neutrophils with vascular congestion and diffuse hemosiderin, H&E ×200; inset of vestibular Perls confirms plentiful hemosiderin, ×200. B, DIV: vaginal biopsy with 1 large (thick arrow) and 1 small (thin arrow) focus of thinned spongiotic epithelium overlying dense nonconfluent papillary infiltrate and vascular congestion, H&E ×40. C, largest focus shows unobscured basal layer and dense lymphocytic infiltrate lacking hemorrhage or hemosiderin confirmed by negative Perls (not shown), H&E ×100.
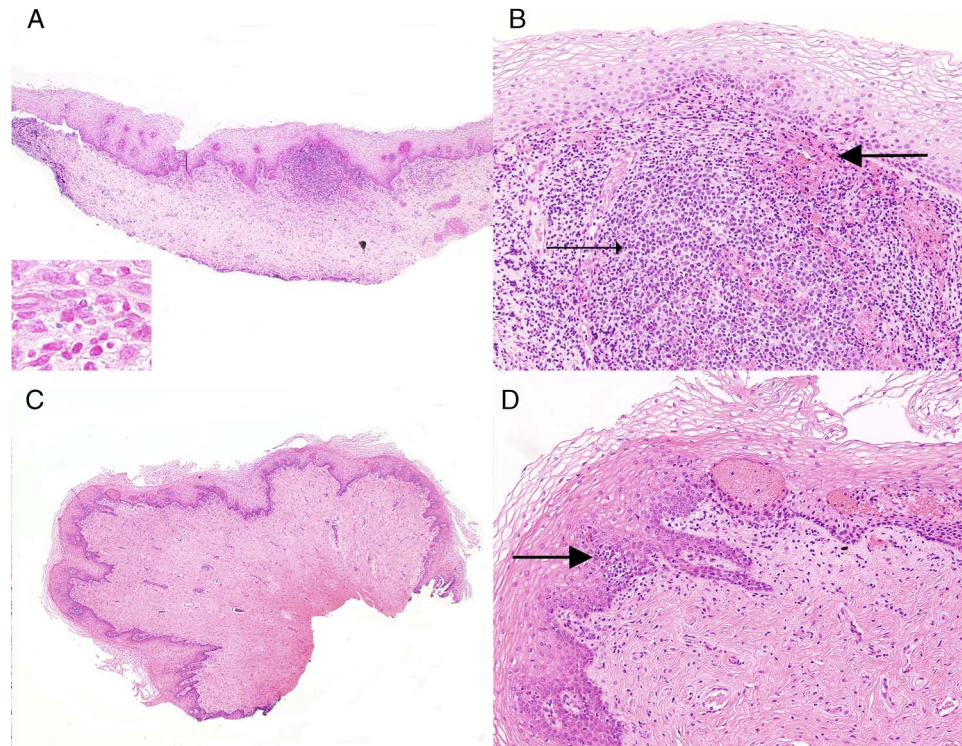
FIGURE 4. A, Severe DIV in a 40-year-old patient with pain, copious discharge, and vaginal red macules seen histologically as multiple foci of thinned epithelium over papillae containing dense infiltrate, hemorrhage, and vascular congestion, H&E ×20; inset of vaginal Perls with minimal hemosiderin, ×400. B, Severe DIV: epithelium shows unobscured basal layer and focal hemorrhage, stroma contains a large hemorrhagic reactive lymphoid nodule (thin arrow), scattered plasma cells, and blobs of hemorrhage (thick arrow), H&E ×100. C, Mild DIV in a 36-year-old with pain, abnormal discharge, and nonerythematous vagina, seen histologically as well-estrogenized vaginal epithelium with multiple small foci of hemorrhage, H&E ×40. D, Focally obscured basal layer (arrow) with exocytosis and intraepithelial hemorrhage; stroma contains mild lymphoplasmacytic infiltrate and vascular congestion with absent hemosiderin confirmed by negative Perls (not shown), H&E ×100.

overlying the foci of inflammation." However, his series was restricted to women with erythematous papules, whereas this study contains a range of presentations and their correspondingly varied histologic findings.

Although DIV and PCV had overlap of clinical findings, histologic DIV did not occur at biopsies obtained from MCJ. Differences in distribution and content of inflammation likely signal site-related differences in local mucosal immune system structure and function. In contrast to vagina, vestibule is replete with mucosa-associated lymphoid tissue and may have a lymphoplasmacytic infiltrate in absence of disease, especially at vestibular gland openings.[15,21] Plasma cells are normally present at orifices, and many vulvar conditions increase plasma cell numbers to include subacute dermatitis, LS, LP, drug reactions, syphilis, cutaneous lupus, and morphea.[11,12,22] The implications of plasma cell density at orificial sites remains unclear.

There may be parallel site-related patterns in the orogastric tract. Desquamative inflammatory vaginitis shows similar histologic features to lymphocytic esophagitis, a recently described condition characterized by dysphagia and histology showing peripapillary spongiosis with multifocal dense lymphocytic infiltrate.[23] It is hypothesized to be an expression of immune dysregulation, often occurring in association with hypothyroidism, Crohn disease, celiac disease, and LP. Papillae are the closest interface between stromal capillaries and epithelium, representing the gateway for response to antigenic challenges. In the mouth, plasma cell gingivostomatitis presents with pain, bleeding, and variable erythematous patches or plaques. Histology shows eroded, sometimes atrophic epithelium

overlying a dense plasma-rich band-like infiltrate. Compared with analogous genital conditions, vascular manifestations are lacking in oral disease.[6,24] Like DIV and PCV, lymphocytic esophagitis and plasma cell gingivostomatitis are considered mysterious disorders with female predominance thought to be reactive phenomena associated with immunologic dysfunction.[6,23,24]

Several additional findings suggest that DIV and PCV exist along a severity spectrum. Some DIV cases were incidental or mild and lacked vulvar manifestations, whereas most PCV cases had severe symptoms and extensive vulvovaginal involvement. Desquamative inflammatory vaginitis histopathology ranges from minimal focal lesions to multifocal dense hemorrhagic inflammation, whereas PCV more uniformly demonstrates confluent marked inflammation and hemorrhage in stages of evolution. A unifying nomenclature may help clinicians and pathologists recognize these as a single phenomenon and facilitate research on etiology, identification, and management. The term "hemorrhagic vestibulovaginitis" describes a spectrum of disease identified by this and previous studies.[4,17–20] The "hemorrhagic" component of the term refers to microscopic features of vascular congestion, fresh hemorrhage, and hemosiderin; hemorrhage is not clinically apparent in milder DIV cases. This terminology is not intended to replace traditional labels of DIV and PCV; rather, it provides an intellectual framework to improve recognition and treatment. Three practice points may assist in management of hemorrhagic vestibulovaginitis:

1. Elicitation of historic triggers aids patient counseling and mitigation of provoking factors may facilitate disease resolution,

2. When clinicians suspect DIV, inspection of vulvar skin and consideration of biopsy may help identify PCV and distinguish it from other dermatologic disorders,

3. When clinicians suspect PCV, speculum examination is advisable and patients may benefit from treatment at vagina and vulva.

It is uncertain whether DIV occurs as an incidental finding or whether this instead reflects provider-level variation. Most DIV biopsies were obtained by general gynecologists in various care settings, whereas most PCV cases were seen in vulvar clinics. Referral to gynecology occurs for myriad indications, so history may not focus on vulvovaginal symptoms and examination may be approached with a colposcopic rather than dermatologic framework. Some colposcopy publications describe "leopard skin" appearance and "colpitis macularis" in reference to trichomoniasis without mention of DIV, but the former is rare in urban Australia, whereas DIV is responsible for up to 7% of presentations for chronic vulvovaginal symptoms.[2,25–29] The 21% rate of DIV nontreatment may result from nonelicitation of symptoms, inability to interpret examination findings, and/or unfamiliarity with the histopathologic diagnosis. This highlights the need for enhanced education on vulvovaginal disease in gynecology and colposcopy training programs.[30,31]

This study also permits elaboration of clinicopathologic diagnostic criteria for DIV and PCV:

1. Focal or confluent erythema or petechiae of the vagina and vestibule, not attributable to an infectious etiology

2. Thinned and/or eroded epithelium overlying an inflammatory infiltrate predominantly comprised of lymphocytes and/or plasma cells.

3. (a) DIV: papillary lymphocyte-predominant infiltrate and lesion width usually <2 mm and (b) PCV: moderate to dense lymphoplasmacytic infiltrate and lesion width usually 2 mm or greater.

4. Vascular congestion, hemorrhage in epithelium and/or stroma, and/or stromal hemosiderin.

Gynecologic pathologists should be aware that colposcopists may provide vaginal specimens noting scattered acetowhite change or poor Lugol uptake. If histopathology excludes HPV-related disease and instead suggests DIV, a short comment may improve clinicians' understanding that this is a known and treatable disorder.

Study limitations are those inherent to retrospective design: missing clinical data, practice variation, and incomplete follow-up. Testing for trichomonas is not routine in urban Australian gynecologic practices due to low prevalence but in other settings is important to exclude this major differential diagnosis for DIV.[27] Point-of-care microscopy is also not undertaken routinely by Australian gynecologists.[3] This practice pattern stands in contrast to routine wet mount performance in Europe and North America and is the likely reason the Australian setting provided sufficient vaginal biopsies to perform the study. Clinician preference to sample 1 location likely underestimated the rate of biopsy-confirmed dual-site disease.

CONCLUSIONS

In summary, DIV and PCV represent points on a spectrum of hemorrhagic vestibulovaginitis with variation influenced by site and severity. Diagnosis, treatment, and research may benefit from this unified conceptualization and corresponding clinicopathologic diagnostic criteria.

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