Symptoms in Plasma Cell Vulvitis: First Observational Cohort Study on Type, Frequency and Severity

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Key Words
Plasma cell vulvitis · Zoon’s vulvitis · Symptoms · Itching · Burning · Dyspareunia

Abstract
Background: Studies assessing symptoms of plasma cell vulvitis (PCV) are lacking. Objectives: To assess the prevalence and severity of PCV-related symptoms and identify possible associations between patient characteristics, clinical features of PCV and treatments administered before a definitive diagnosis. Methods: Thirty-six patients affected with PCV were included. Data were collected by direct interview and clinical examination. Results: Thirty patients (83.3%) complained of symptoms: burning was the most frequent (80.6%) while dyspareunia was the severest. Of the symptomatic patients, 73.3% experienced severe symptoms. Severity of symptoms was not associated with age at onset and duration of PCV. Almost 70% of the patients had previously undergone treatments. Conclusions: Symptoms in PCV are frequent and more than often severe. Neither age at onset nor duration of the disease nor the extent of vulvar involvement were associated with symptom severity. Both the delay in diagnosis and the inappropriate previous treatments seem to indicate frequent misdiagnosis.

Introduction
Plasma cell vulvitis (PCV) or Zoon’s vulvitis is an uncommon chronic, inflammatory disease which owes its name to the characteristic plasma cell infiltrate. It is an entirely benign disorder, but it can cause local discomfort and render differential diagnosis with other vulvar disorders difficult [1–5].

No effective treatment regimens have been established. A wide range of therapeutic options have been proposed [1, 2, 6–18].

To date only case reports and small series of PCV have been reported in the literature but exhaustive epidemiological data are lacking. In particular, no previous studies have specifically addressed prevalence, type and severity of PCV-related symptoms.

The main aim of the present study was to assess the demographic and clinical features of a large population of women affected with PCV, mainly focusing on disease symptoms.

Patients and Methods

Study Design and Objectives
We conducted a retrospective observational study in the setting of a cohort of patients affected with PCV attending the Vulva Unit of the Dermatology Section of the University of Ferrara, Italy, be-
Bulb, the introitus, the clitoris and the fourchette were the typical face of the labia minora and the periurethral area but also the vestigial patches with a faint orange hue affecting mainly the inner surface, well-circumscribed glistening, glazed, single or multiple erythematous spots (‘Cayenne pepper spots’) and erosive lesions were supportive helpful features in formulating the diagnosis were: epithelial atrophy, lozenge-shaped keratinocytes, slight spongiosis associated with vascular dilatation, erythrocyte extravasation and haemosiderin deposition [4]. The presence of <25% plasma cells was considered nonspecific. Patients were excluded from the study in the presence of: (i) lack of histological confirmation; (ii) clinical or histological features showing possible resemblance with other diseases, such as lichen planus or lichen sclerosus; (iii) lack of agreement between clinical and histological features; (iv) history of trauma or factitial causes; (v) concomitant active vulvar infectious diseases; (vi) pregnancy and breast-feeding. In order to avoid misinterpretation of PCV-related symptoms, patients were arbitrarily excluded from the study in the presence of systemic and/or topical PCV treatments during the 4 weeks before enrolment. Refusal or inability to reply to the questions during the interview were further exclusion criteria. All data were recorded in a standardized data collection form.

Thirty-six out of 42 screened patients were eligible for the present study. Six patients were not included as they failed to meet eligibility criteria.

Data Collection
A standardized data collection form was elaborated to collect from the hospital clinical records the following: (1) patient age when clinical and histological diagnosis of PCV was established; (2) age at onset of PCV (age when the women first experienced PCV-related symptoms or noticed disease signs); (3) delay in diagnosis, recorded as the time (in months) between the patient-reported onset of signs and/or symptoms and the definite diagnosis; this corresponds to the duration of the disease before diagnosis; (4) medical or non-pharmacological therapies used for treating PCV prior to diagnosis; (5) anatomical parts of the vulva involved by PCV, meant as number of different anatomical sites affected; (6) PCV-related symptoms.

Study Procedures and Assessment
The presence or absence of the 3 symptoms itching, burning and dyspareunia (the latter only when applicable) was investigated by interview using a visual analogue scale; a score of 10 was attributed to the highest intensity of the symptoms and 0 to their absence. Patients were asked to specify the number and severity of the symptoms they experienced at the moment of the interview. A global subjective score (GSS) was obtained by summing each symptom parameter (highest GSS = 30) in order to ease statistical analysis [20–22]. Patients were arbitrarily subdivided according to the severity of symptoms into 3 main groups: (i) mild, when GSS was ≤5, (ii) moderate, when GSS was 6–9, and (iii) severe, when GSS was ≥10. These cut-offs were defined, in accordance with our clinical experience, by patient discomfort and quality of life impairment, as previously reported [22].

Statistical Analyses
Binary data were analysed with χ² or exact Fisher’s test according to conditions. Quantitative data were analysed by means of a t test, in the case of normality and equal variance (homoscedasticity), or, alternatively, by means of the Mann-Whitney U test. Normality of groups was assessed by the Kolmogorov-Smirnov test; homoscedasticity of groups was assessed by Levene’s test and the Brown-Forsythe test. Statistical significance was defined as p < 0.05.
Results

Patient Characteristics
Demographic and clinical data of the 36 women affected with PCV included in the study are reported in table 1.

Clinical Symptoms and Vulvar Involvement
Symptoms at inclusion were present in 30 patients (83.3%); 6 patients (16.7%) were asymptomatic (table 1). The most frequently reported symptom was burning (29 patients, 80.6% of total), while 16 patients (44.4%) complained of itching (table 2). Ten women (27.8%) stated that dyspareunia was not a pertinent symptom in their everyday life; among the remaining 26 patients, 19 (73.1%) reported dyspareunia (table 2). The mean severity of symptoms is reported in table 3. Based on the protocol-defined overall symptom severity, 5 patients had mild symptoms (13.9% of enrolled population, 16.7% of symptomatic patients), 3 moderate (8.3%, i.e. 10% of symptomatic patients), and 22 severe (61.1%, i.e. 73.3% of symptomatic women) (table 1).

Anatomical sites involved by PCV are reported in table 2. It could be useful to clarify that the vulvar vestibule is the portion of the vulva that extends from the exterior surface of the hymen to the frenulum of the clitoris anteriorly, fourchette posteriorly and laterally to Hart’s line (border between keratinized and non-keratinized epithelium of the labia minora). The introitus is the vaginal opening (or meatus or orifice) and is localized within the vestibule. The fourchette is a small fold of membrane connecting the labia minora in the posterior part of the vulva.

Previous Treatments
Twelve patients (33.3%) had not undergone previous treatments. The treatments reported by the other 24 patients (66.7%) are given in table 3. Among the 30 symptomatic patients, 22 (73.3%) had undergone previous pharmacological treatments, whereas only 1 (16.7%) among the asymptomatic patients had received therapies prior to diagnosis. The rate of previously treated patients between symptomatic and asymptomatic subjects was found to be significantly different (p = 0.016, exact Fisher’s test). No patient was treated with surgery.

Associations
In our cohort, the extent of vulvar involvement (number of vulvar parts affected by the disease) was not associ-
ated with severity of symptoms at diagnosis (p = 0.161, $\chi^2$ test). Both mean age at diagnosis and duration of the disease before diagnosis were higher in asymptomatic patients, but not significantly so (p = 0.45 according to t test and p = 0.24 according to Mann-Whitney U test, respectively). Among the study patients, the severity of PCV symptoms was not significantly associated with either age at disease onset (p = 0.153, t test) or age at diagnosis (p = 0.220, t test).

**Discussion**

The incidence of PCV is unknown, as well as its aetio-pathogenesis, although a variety of triggering factors have been hypothesized [1–5, 19]. The presence of a lichenoid infiltrate containing a predominance of plasma cells as a distinctive histological marker suggests a polyclonal stimulation of B cells [23].

PCV is not universally considered a distinct condition, in fact many vulvar diseases share clinical features with PCV and, on histological examination, a plasma cell infiltrate can be found as a non-specific inflammatory pattern [24]. In spite of this, we consider PCV a well-defined clinicopathological entity. Indeed, in the presence of both the typical clinical features (fig. 1), and histological findings, in particular a percentage of plasma cells in the dermal infiltrate >50% [4], without genital and extragenital clinicopathological aspects resembling other diseases, a diagnosis of PCV can reasonably be made. With regard to our study patients, the accuracy of the diagnosis of PCV was determined by both clinical and histological features.

The mean age at onset of vulvar lichen sclerosus (VLS) in our population was about 49 years, which is consistent with other reports, although the condition has been reported in the third to ninth decade of life [1–5] and a unique case has been described in an 8-year-old-girl [25].

In our patients there was considerable delay in diagnosis after onset of symptoms (mean 55.4 months, standard deviation 70.7 months). The reasons for delay have not been addressed in this study. However, it may be speculated that the disease location on intimate places, which may cause embarrassment, may lead to a delay in medical consultation. Misdiagnosis and non-diagnosis by physicians unfamiliar with the condition could represent further reasons for the delay in diagnosis. Finding that diagnosis in asymptomatic patients was deferred, on average, for about 4 years compared to symptomatic ones, even though without a statistically significant difference, seems to suggest that absence of symptoms delays PCV diagnosis. A correspondence between patient-reported onset of symptoms and true duration of the disease can be supposed based on persistence of the same symptoms.

About 73% of the study patients had undergone medical or non-pharmacological treatments prior to attending at our Vulva Unit. Topical corticosteroids were found to be the most common intervention (58.3% of the previously treated patients), followed by emollients (45.8%). Even though antimicrobial agents have been used in a few reported PCV cases with encouraging results [26], finding that 25% of patients had been treated with topical and/or systemic antimycotic agents, and 20.8% with antibiotics, seems rather to suggest that PCV is a frequently misdiagnosed disorder. Despite the lack of evidence for the efficacy of topical oestrogens in the treatment of PCV, about 16% of the included patients had been treated with topical and/or systemic antimycotic agents, and 20.8% with antibiotics, seems rather to suggest that PCV is a frequently misdiagnosed disorder. Despite the lack of evidence for the efficacy of topical oestrogens in the treatment of PCV, about 16% of the included patients had been treated with such therapies. On the other hand, even though topical tacrolimus and pimecrolimus have been shown to be an effective and well-tolerated therapeutic option in the treatment of PCV, and so in the case of plasma cell balanitis [2, 27], only 8.3% of patients had previously been treated with topical calcineurin inhibitors. Among treated patients, 47.2% reported more than one previous treatment. This could mirror the chronic course of the disease,

<table>
<thead>
<tr>
<th>Table 3. Previous topical therapies for PCV</th>
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<tr>
<td>Number of previous therapies</td>
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<tr>
<td>None</td>
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<td>At least 1</td>
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<td>More than 2</td>
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<td>Previous therapies</td>
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<td>Topical corticosteroids</td>
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<td>Topical and/or systemic antimycotics</td>
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<td>Topical and/or systemic antibiotics</td>
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<td>Topical phyto-oestrogens</td>
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<td>Topical calcineurin inhibitors</td>
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<tr>
<td>Emollients and moisturizers</td>
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<td>Vaginal suppositories, douches</td>
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<td>Previous pharmacological treatments</td>
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<td>Asymptomatic patients</td>
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<td>Symptomatic patients</td>
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<td>Figures in brackets are percentages calculated on previously treated patients (n = 24).</td>
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<td>As some patients had undergone multiple treatments, the total of therapies is greater than the number of patients enrolled in the study.</td>
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as well as a tendency to change treatment due to poor response to therapy. Since a significant majority of symptomatic patients (73.3%) had been treated before diagnosis in comparison with only 16.7% of asymptomatic patients, it may be argued that disease-related symptoms represent the main troublesome feature of the disease and the main reason for requiring treatment.

In our study patients, the introitus was the commonest site involved by the disease (table 3). In more than half of the patients, PCV affected more than 1 anatomical site. No patients had vaginal involvement.

Eighty-three percent of the study population complained of symptoms. Burning was the most common symptom affecting more than 80 of the subjects; 44% of women complained of itching. Dyspareunia was not evaluable in 10 patients (27.8% of the total); however, 73.1% of the women who had sexual intercourse reported having dyspareunia. Moreover, among the assessed symptoms, dyspareunia had the highest mean severity score. The majority of patients (61.1%) reported severe PCV-related symptoms. Taken together, these data strongly suggest a dramatic impact on the quality of life of patients affected with PCV. In our patients, symptom severity was not associated either with the extent of vulvar involvement or age at PCV onset.

Comparing the present findings with our previous epidemiological study on VLS, we can observe that PCV tends to begin earlier and take longer to diagnose than VLS [22]. To explain this latter finding, it may be hypothesized that patients with PCV present more than those with VLS with non-specific clinical features and, on the whole, PCV affects patients less severely, in terms of symptoms, leading probably to a less urgent request for medical consultation. In fact, concerning the symptom profile of the diseases, both the rate of symptomatic patients and the percentage of women complaining of severe symptoms was found to be higher in VLS patients when compared with PCV patients. While burning was the most typical symptom related to PCV, itching was found to be the commonest symptom reported by VLS patients.

The results reported herein should be viewed in the light of the limitations of the study, such as its retrospective design and the relatively small number of patients. Furthermore, univocal methods for the assessment of PCV severity are not available and severity grades and cut-offs in the present study have been arbitrarily defined. However, up to now our cohort of patients is the largest ever reported and this is the first study to specifically address the symptomatic profile of the disease.

We can thus conclude that the large majority of patients affected by PCV complain of symptoms, in particular burning. The reported PCV-related symptoms are usually severe and may affect patient quality of life. Both the delay in diagnosis observed and the inappropriate treatments often received by patients seem to indicate frequent misdiagnosis or non-diagnosis and the lack of treatment guidelines.

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## Disclosure Statement

The authors report no conflicts of interest and make no financial disclosure.
