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A RETROSPECTIVE STUDY OF 129 PATIENTS WITH PLASMA CELL BALANITIS

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Anniina Jormanainen : A retrospective study of 129 patients with plasma cell balanitis
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Plasmasolubalaniitti (PCB, Plasma cell balanitis) on terskan ja esinahan krooninen ihotulehdus, joka näyttäytyy tyypillisesti tarkkarajaisena kirkkaanpunaisena kiiltävänä läiskänä. Tutkimustieto PCB:stä on niukkaa ja pohjautuu tapausselostuksiin ja -sarjoihin. PCB:n etiologia, ilmaantuvuus ja esiintyvyys ovat toistaiseksi tuntemattomia. Ympärileikkaus on hoidon kultainen standardi. Paikallishoitoja, kuten paikallisia kortikosteroideja, kalsineuriiniestäjiä, fusidiinihappoa ja imikimodia, on käytetty laajalti, mutta tieteellinen näyttö niiden tehosta on puutteellista.

Tässä retrospektiivisessä tutkimuksessa tutkittiin 129:ää PCB diagnoosin saanutta potilasta Tampereen yliopistollisen sairaalan ihotautien yksikössä aikavälillä 1. tammikuuta 2003–31. joulukuuta 2018. Tutkimuksen tavoite oli tutkia PCB:n kliinistä profiilia, hoitomuotoja ja lopputuloksia suhteellisen suuressa kohortissa.

Suurempaa osaa potilaista hoidettiin ainoastaan paikallisilla valmisteilla, vaikkakin 31 potilasta (24 %) lopulta päätyi ympärileikkaukseen. Käytetyimmät ja tehokkaimmat paikallisvalmisteet olivat takrolimuusi (0,03 % tai 0,1 %) ja klobetasolipropionaatti. Seuranta-aika oli lyhyempi (mediaani 8 kuukautta vs. 47 kuukautta, P=0,002) niillä, joiden hoitona oli ympärileikkaus ja ne myös todennäköisemmin saavuttivat remission (46 % vs. 16 %, P=0.002) verrattuna niihin, joiden hoitolinja oli konservatiivinen. Vaikeampioireisia hoidettiin useammalla eri hoidolla, useammin ympärileikkauksella, ja ne todennäköisemmin saavuttivat remission. Seuranta-aika oli pidempi niillä, joilla oli histopatologinen diagnoosi kuin kliininen diagnoosi (mediaani 16 kuukautta vs. 6 kuukautta, P=0,01).

Paikallishoidot ovat harvoin kuratiivisia, mutta niistä takrolimuusilla ja paikallisilla kortikosteroideilla on suurin näyttö tehosta. Remissioaste on huomattavasti parempi ympärileikatuilla ja sitä tulisi harkita hoitomuotona jo varhaisessa vaiheessa. Lisää tutkimuksia plasmasolubalaniitista tarvitaan parhaan hoitokäytännön löytämiseksi.

Avainsanat: Plasmasolubalaniitti, Zoonin balaniitti, hoito, ympärileikkaus

ABSTRACT

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Plasma cell balanitis (PCB) is a chronic inflammatory dermatosis of the glans penis and prepuce, typically presenting as discrete shiny bright red plaques. Research on PCB is scarce, with case reports and small series. The aetiology, incidence and prevalence of PCB remains unclear. Circumcision is considered as the treatment of choice. Topical treatments such as topical corticosteroids, calcineurin inhibitors, fucidic acid and imiquimod have been widely used, but lack evidence of efficacy.

The objective of this study was to investigate the clinical profiles, treatment methods and outcomes of PCB patients in a relatively large cohort.

We concluded a retrospective study of 129 patients with the diagnosis of PCB between the 1st of January 2003 and the 31st of December 2018 in Tampere University Hospital (TAYS) dermatology department.

Greater number of patients were treated with topical treatments only, whilst 31 patients (24 %) eventually underwent circumcision. The most used and most effective topical treatments were tacrolimus (0.03 % or 0.1 %) and clobetasol propionate. Those treated with circumcision had a shorter follow-up time (median 8 months vs 47 months, P=0.002) and were more likely to reach remission (46 % vs 16 %, P=0.002) compared to those treated with only topical treatments. Patients with more severe symptoms were treated more often with several topical treatments, with circumcision and were more likely to reach remission in the end. Follow-up time was longer among patients with histopathologic diagnosis than with a clinical diagnosis (median 16 months vs 6 months, P=0.01).

Topical treatments are rarely curative, but among them tacrolimus and topical corticosteroids show the strongest evidence of efficacy. Rate of remission is significantly better among circumcised and is to be considered already at an early stage. Further studies are needed to find the best management of care for PCB.

Keywords: Plasma cell balanitis, Zoon’s balanitis, treatment, circumcision

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Introduction

Plasma cell balanitis (PCB), also called Zoon's balanitis, is an uncommon chronic but benign inflammatory dermatosis of the glans penis, the coronal sulcus, and the prepuce. It affects mostly uncircumcised men as it normally occurs between two mucous membranes. The aetiology of PCB remains unclear, but considering its location and circumcision often having a curative effect, irritation has been proposed to play a significant role [1]. There is no supportive evidence for chronic inflammation caused by pathogens [2]. The incidence and prevalence of PCB in the general population is unknown. Due to PCB's asymptomacy, social stigma and difficulty of clinical diagnosis, PCB is presumably underdiagnosed. An analogous condition in women, plasma cell vulvitis, is even more uncommon. [1,2]

The first eight cases of PCB were recorded by Zoon in 1952 when he notified the presence of plasma cells in a bandlike infiltrate in the upper dermis [3]. Plasma cells are not abundant in all cases and their density can be variable. Other histological features include thinned or even absent epidermis with diamond- or lozenge-shaped flattened keratinocytes, as well as vascular proliferation and dilation. Extravasation of erythrocytes and hemosiderin can also be seen. Clinically PCB manifests as discrete erythematous, shiny, moist plaques, generally bright red coloured or with cayenne pepper-coloured spots. Kissing lesions involving adjacent touching areas are typical. Whilst often asymptomatic, possible symptoms may include pain, negative impact on sexual functions, burning sensation, pruritus, discharge, and erosions with the tendency to bleed. [1,4–6]

Diagnosis of PCB can be clinical or confirmed by typical histopathological findings. The following clinical diagnosis criteria have been proposed: shiny erythematous patches present for over three months, absence of lichen planus and concurrent infections, and poor

response to topical therapies [1]. It is important to differentiate PCB from other clinically similar inflammatory penile dermatoses. The foremost is Penile intraepithelial neoplasia, PIN (Erythroplasia of Queyrat, Bowen's disease of penis) as it is a premalignant condition with risk of invasive cancer. Others are erosive lichen planus, allergic contact dermatitis, psoriasis, candida balanitis, extramammary Paget's disease, herpes simplex virus, lupus erythematosus, mucosal pemphigoid, plasmacytoma, primary syphilis, pseudoepitheliomatous keratotic and micaceous balanitis and squamous cell carcinoma [5,7]. Circumcision has been considered as treatment of choice for PCB [5,8]. Topical treatments are widely used despite the lack of strong evidence of efficacy, as their efficacy is based on case reports with limited follow-up [9–11]. Topical corticosteroids, calcineurin inhibitors, fucidic acid and imiquimod among others have shown some clinical benefit. Other less invasive surgical modalities have been used to treat PCB in previous reports with varying success, such as carbon dioxide laser (CO_2), Erbium (Er):YAG laser and photodynamic therapy [2,12,13].

Knowledge of the disease is insufficient and research on PCB is scarce, with most of the published studies being case reports and only a few studies with more than 20 patients have been published. The objective of this study was to investigate the clinical profiles, treatment methods and outcomes of PCB patients in a representative cohort from a regional referral hospital in Finland.

Materials and methods

A retrospective study of patients with the diagnosis PCB between the 1st of January 2003 and the 31st of December 2018 in Tampere University Hospital (TAYS) dermatology department was carried out. Inclusion criteria were male sex, age above 18 years and a clinical or histopathological diagnosis of PCB. The following data were collected from patient records:

age at the onset of symptoms, date of arrival at clinic, age at diagnosis, diagnosis delay calculated from the onset of symptoms to the diagnosis of PCB, histopathological confirmation, severity of symptoms, used treatments (methods, duration and outcome), previous medical history, body-mass index (BMI), and the follow-up time at the department of dermatology.

Symptom severity was roughly divided by the researcher into three categories based on patient records. The severity was recorded as mild if the symptoms were mostly aesthetic, moderate if occasional pain and other discomfort was reported, and severe if pain, discomfort, and burden were frequent. Efficacy of the treatment was measured by complete remission of the lesions, partial remission (noticeable improvement) or failure (no improvement or worsening). As data were not normally distributed, median values and interquartile ranges were used as descriptives. The $\chi 2$ test and Fisher's exact test were used in cross-tabulations, and the Mann–Whitney U and Kruskal–Wallis H test were used for comparing continuous variables. All testing was two-sided and $p < 0.05$ was considered statistically significant. All the statistical analyses were performed with SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. USA). The study was approved by the Ethics Committee of Tampere University Hospital, Finland.

Results

We found patient records of 129 men with a clinical or histopathological diagnosis of PCB. Their clinical profile is summarized in Table 1.

In total, 31 patients (24 %) were eventually treated with circumcision as others were treated with only topical treatments. The most common topical treatments used were tacrolimus 0.03 % or 0.1 %, clobetasol propionate, and those were also the most effective ones (Table

2). Other commonly used treatments were fucidic acid 2 %, a combination of econazole nitrate 1 % + triamcinolone acetonide 0.1 % and betamethasone dipropionate, but those were less effective. Carbon dioxide laser was used for eight patients to treat adhesions, but was not used as a primary therapeutic treatment, since our earlier experience was disappointing for long-time results. Mupirocin ointment was used for two patients, with one treatment failure, and the other treatment still ongoing at the end of the study. During the follow-up at the department, 25 patients (19 %) reached total remission, and the remission was more common among the circumcised patients compared with those treated only with topical treatments (46 % vs 16 %, p=0.002). A statistically significant difference in the follow-up time between circumcised and non-circumcised (median 47 months vs 8 months, P=0.002) was found. There was no association between treatment efficacy and BMI or obesity (BMI > 25).

The clinical picture of the disease and used treatments were compared across the severity of the disease (Table 3). There was a non-significant trend with more severe disease and younger age at disease onset. The BMI or concomitant diabetes mellitus did not associate with the disease severity. The patients with more severe symptoms were treated more often with several topical treatments, and they were also treated more often with circumcision. In the end, remission was significantly more common among those with severe symptoms.

To assess the accuracy of the clinical diagnosis, the patients were divided into clinical diagnosis group (CDG) and histopathological diagnosis group (HDG). There were no statistical differences between the two groups in age at the onset of symptoms, in time to diagnosis from symptoms, in severity of symptoms nor in outcome. There was however a statistically significant difference in the follow-up time between HDG and CDG (median 16 months vs 6

months, P=0.01). Treatment efficacies were similar in the two groups, except with topical Econazole Nitrate 1 % + Triamcinolone Acetonide 0.1 %, where CDG experienced greater benefit from the treatment (P=0.024).

Discussion

Treatment of PCB is very challenging due to its chronic nature. In our study the degree of remission was significantly better among circumcised in comparison to those treated only with topical treatments (46% vs 16%). Our results are in concordant with previous studies, in which circumcision has been considered as method of choice [1,4,5,8,14,15]. In the contrary, compared to earlier published results having almost total remission rate for circumcision, our remission rate was much lower. For this we have no obvious explanation. One possible cause is that topical therapy was the primary therapy for all patients, and circumcision was only done for difficult to treat patients. Based on our clinical observations, the two foremost reasons for failure were obesity and circumcisions done in effort to preserve the prepuce. The latter was seen in a few cases and in one of these cases, the renewed circumcision was curative. Due to obesity, the glans of the penis withdraws inside the visceral fat of the lower abdominal area, which preserves the optimal moist environment for PCB. We also showed that PCB can appear in circumcised male, which could similarly be explained by obesity. A case report of a circumcised and HIV infected male with PCB has been published, but to date there are no other reports on circumcised patients with PCB [16].

Data on comparison of different topical treatments is scarce. Topicals used based on published studies are corticosteroids, trimovate (oxytetracycline 3 % and clobetasone butyrate 0,05 %), calcineurin inhibitors (tacrolimus 0,1 % and 0.03 % and pimecrolimus 1 %), imiquimod 5 %, fucidic acid 2 % and mupirocin [2,10,11,17–20]. Topical treatments are palliative,

but rarely curative. It is common for them to initially have some effect in improving the symptoms, but progressive use or cessation often results in lack of efficacy or relapse, which was also seen in our study. Based on our study, the topicals with best results were clobetasol propionate and tacrolimus. In two reports published in 2017 mupirocin was successfully used to treat PCB altogether in three patients [19,20]. In this study mupirocin was only used as treatment towards the end of the study period, with only two patients and a short follow up time. Since there was no systematic approach in choosing the topical therapy in this study, the results should naturally be interpreted with care.

Diagnosis of PCB is usually confirmed by skin biopsy with typical histological findings of PCB. In our study the clinical (CDG) and histopathologic (HDG) diagnosis groups were similar, except in the follow-up time and treatment efficacy of Econazole Nitrate 1 % + Triamcinolone Acetonide 0.1 %. These differences could be explained by their initial response to treatment. The patients in CDG might response to treatment more favourably, be satisfied with partial remission of symptoms and have no need for longer follow-up. Whereas patients with a more treatment resistant disease remain in follow-up longer and a histopathologic diagnosis is made more frequently.

Severity of the disease was associated with a longer follow-up time (although statistically non-significant due to a relatively small sample size) and a higher number of treatments used. With a severe and persistent disease more topicals are tried, and once turning out to be inefficient, a greater number of patients eventually undergo circumcision. Inefficient treatment trials and prolonged follow-up needlessly increase the burden of disease for the patient and the healthcare. A failed trial with the most effective topical treatments,

corticosteroids and tacrolimus, should quickly lead to consideration of circumcision especially in a more severe disease.

To date there are very few large cohort studies published of PCB patients. The aim of this study was to increase knowledge of the disease profile, treatment, and outcomes to facilitate the standardization of care. We feel that this large cohort of patients with PCB at a single site and study gives valuable new information on PCB. It also emphasizes the chronic nature of PCB and gives some tools in comparing different treatments. The retrospective design, with some missing data, and retrospective assessment of treatment efficacy limits the interpretation of the results.

In conclusion, a suspicion of PCB should lead to histopathologic diagnostic procedures without unnecessary delay to minimize the time to diagnosis and effective treatment. The treatment of choice is circumcision; hence a discussion of surgical procedure should take place already at an early stage. Non-surgical, mostly palliative options are topical corticosteroids and tacrolimus. Further studies are needed to find the best management of care for PCB.

Tables

Table 1. Clinical profile of patients

	Sample size	Median	IQR*	Range
Age at onset of symptoms, years	117	60	49–69	16—82
Age at diagnosis, years	126	64	54–71	17—92
Diagnostic delay from the onset of symptoms, months	114	13	5–38	0—285
Follow-up time at the clinic**, months	113	11	3–34	0—192
Diagnostic pathologic sample, HDG***	82	-	-	-
Body mass index, kg/m^2	77	27.7	24.7–32.0	15.4—41.5

* Interquartile range (IQR)
** At the time of the data collection, 10 % (n=13) of the patients were still being followed at the clinic and 3 % (n=4) visited the clinic only once.
*** Histopathological diagnosis group (HDG)

Table 2. Efficacy of treatments

	Tacrolimus 0.03 % or 0.1 %	Clobetasol propionate	Fucidin 2 %	Econazole Nitrate 1 % + Triamcinolone Acetonide 0.1 %	Betamethasone Dipropionate	Circumcision
Number of cases	75	84	25	39	26	31
Number of cases with known outcome	67	75	22	36	24	27
Efficacy, n (%)						
Remission	2 (3)	9 (12)	0	3 (8)	0	12 (44)
Partial remission	41 (61)	45 (60)	11 (50)	13 (36)	11 (46)	8 (30*)
Nonresponse	24 (36)	21 (28)	11 (50)	20 (56)	13 (54)	7 (26)

In use after follow-up, n (%)	33 (44)	31 (37)	3 (12)	5 (13)	5 (19)	-

* Requires topical maintenance treatment

Table 3. Symptom severity

	Mild, n=60	Moderate, n=47	Severe, n=20	p-value
Age at onset of symptoms, median (IQR*), years	62 (54–70)	59 (47–67)	53 (47–66)	0.148
Diagnostic delay from the onset of symptoms, median (IQR), months	12 (6-40)	14 (5-50)	20 (1-26)	0.873
Diagnostic pathologic sample, HDG**, n (%)	38 (63)	28 (60)	14 (70)	0.719
Body mass index, median (IQR), kg/m^2	27.2 (24.5–31.1)	30.5 (25.5–32.7)	27.7 (23.7–32.8)	0.334
Diabetes mellitus, n (%)	18 (30)	10 (21)	6 (30)	0.563
Number of topical treatments per patient***, n (%)				0.011
0–1	25 (42)	11 (23)	3 (15)	
2–3	31 (52)	27 (57)	10 (50)	
4–5	4 (7)	9 (19)	7 (35)	
Circumcision, n (%)	3 (5)	13 (28)	12 (63)	<0.001
Follow-up time, median (IQR), months	8 (3-21)	18 (4-50)	22 (3-80)	0.092

Remission, n (%)	6 (13)	11 (28)	7 (39)	0.046

*Interquartile range (IQR)
** Histopathologic diagnosis group (HDG)
***Treatments in Table 2

References

1. Kumar B, Narang T, Dass Radotra B, Gupta S. Plasma cell balanitis: clinicopathologic study of 112 cases and treatment modalities. J Cutan Med Surg. 2006;10:11–5.

2. Dayal S, Sahu P. Zoon balanitis: A comprehensive review. Indian J Sex Transm Dis AIDS. 2016;37:129–38.

3. Zoon JJ. [Chronic benign circumscript plasmocytic balanoposthitis]. Dermatologica. 1952;105:1–7.

4. Kumar B, Sharma R, Rajagopalan M, Radotra BD. Plasma cell balanitis: clinical and histopathological features--response to circumcision. Genitourin Med. 1995;71:32–4.

5. Weyers W, Ende Y, Schalla W, Diaz-Cascajo C. Balanitis of Zoon: a clinicopathologic study of 45 cases. Am J Dermatopathol. 2002;24:459–67.

6. Bolognia J, Jorizzo J, Schaffer J et al. Dermatology, 3rd edition. London: Elsevier; 2012.

7. Jackson S, Nesbitt LT. Differential Diagnosis for the Dermatologist. Berlin, Heidelberg: Springer Berlin Heidelberg; 2008 [cited 2021 Dec 30]. Available from: http://link.springer.com/10.1007/978-3-540-75887-7

8. Kumar B. Circumcision is still the gold standard in management of plasma cell balanitis. Dermatol Ther. 2018;31:12661.

9. Tang A, David N, Horton LW. Plasma cell balanitis of Zoon: response to Trimovate cream. Int J STD AIDS. 2001;12:75–8.

10. Roé E, Dalmau J, Peramiquel L, Pérez M, López-Lozano H, Alomar A. Plasma cell balanitis of zoon treated with topical tacrolimus 0.1%: report of three cases. J Eur Acad Dermatol Venereol. 2007;21:284–5.

11. Stinco G, Piccirillo F, Patrone P. Discordant results with pimecrolimus 1% cream in the treatment of plasma cell balanitis. Dermatol Basel Switz. 2009;218:155–8.

12. Retamar RA, Kien MC, Chouela EN. Zoon's balanitis: presentation of 15 patients, five treated with a carbon dioxide laser. Int J Dermatol. 2003;42:305–7.

13. Borgia F, Vaccaro M, Foti A, Giuffrida R, Cannavò SP. Zoon's balanitis successfully treated with photodynamic therapy: Case report and literature review. Photodiagnosis Photodyn Ther. 2016;13:347–9.

14. Sonnex T, Dawber R, Ryan T, Ralfs I. Zoon's (plasma-cell) balanitis: treatment by circumcision. Br J Dermatol. 1982;106:585–8.

15. Ferrándiz C, Ribera M. Zoon's balanitis treated by circumcision. J Dermatol Surg Oncol. 1984;10:622–5.

16. Adégbidi H, Atadokpèdé F, Dégboé B et al. [Zoon's balanitis in circumcised and HIV infected man, at Cotonou (Benin)]. Bull Soc Pathol Exot 1990. 2014;107:139–41.

17. Daga SO, Wagaskar VG, Jumnake SF, Patwardhan SK. Zoon's balanitis treated with topical tacrolimus. Urol Ann. 2017;9:211–3.

18. Moreno-Arias GA, Camps-Fresneda A, Llaberia C, Palou-Almerich J. Plasma cell balanitis treated with tacrolimus 0.1%. Br J Dermatol. 2005;153:1204–6.

19. Bari O, Cohen PR. Successful Management of Zoon's Balanitis with Topical Mupirocin Ointment: A Case Report and Literature Review of Mupirocin-Responsive Balanitis Circumscripta Plasmacelluaris. Dermatol Ther. 2017;7:203–10.

20. Lee MA, Cohen PR. Zoon Balanitis Revisited: Report of Balanitis Circumscripta Plasmacellularis Resolving With Topical Mupirocin Ointment Monotherapy. J Drugs Dermatol JDD. 2017;16:285–7.