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Zoon Vulvitis Treated Successfully With Platelet-Rich Plasma: First Case Reported

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Zoon vulvitis (also known as plasma cell vulvitis) is a rare benign idiopathic vulvar inflammatory disorder of unknown etiology characterized by a bright-red mucosal lesion of significant chronicity and mainly affecting adult women. It typically appears as atrophic, shiny, erythematous plaques characterized by a dense, subepithelial mononuclear cell infiltrate largely composed of plasma cells.[1] Very few studies of this condition are reported in the literature, and unfortunately, the treatments described show limited success. We report the first case of this condition treated with complete resolution of symptoms using platelet-rich plasma (PRP).

CASE REPORT

A 66-year-old postmenopausal woman was referred to our gynecology department with a 10-year history of vulvar pruritus misdiagnosed as vulvar mycosis and treated several times with antimycotics without any relief of the symptoms. On clinical examination, she was found to have pale atrophic mucosa with an evident u-shaped glistening erythematous halo of her vulvar introitus extending from the lower part of the right labia minora to the lower part of the left labia minora, almost encircling the urethral meatus. No bleeding was reported. There were no fissures, excoriations, or oozing (exudation) or regional lymphadenopathy. The most frequent symptoms were vulvar pruritus, burning, soreness, stinging, vaginal dryness, and introital dyspareunia. The clinical records included 2 pregnancies, resolved by episiotomy, and a history of arterial hypertension and diabetes mellitus type 2. Differential diagnosis included erosive lichen planus, genital psoriasis, lichen sclerosus et atrophicus, and high-grade squamous intraepithelial lesions (Vulvar Intraepithelial Neoplasia III). Laboratory analysis showed no abnormal hemogram or urinalysis variables. Urinary incontinence was not reported. After clinical evaluation, a skin biopsy was taken from the erythematous area. The biopsy specimen of the lesion revealed epidermal thinning, the absence of a horny and granular cell layer, and the presence of distinctive lozenge-shaped keratinocytes with sparse dyskeratosis and spongiosis. Furthermore, a dense dermal subepithelial band-like infiltrate mostly composed of plasma cells (CD138+) as well as a mixed T/B-cell infiltrate (CD3+/CD20+) (see Figures 1A–C) were observed, together with vascular proliferation with dilated vessels and hemosiderin deposition (see Figures 2A, B). Histology did not show any basal cell hydropic degeneration, dermal hyalinization, hyperkeratosis, hypergranulosis, or cytoid bodies. The report stated that these findings were consistent with Zoon vulvitis. Treatment with autologous PRP was prescribed after histological results and obtaining the patient's consent. In 2015, our gynecology department decided to replace topical corticosteroid therapy with platelet-rich plasma as a first line of treatment of chronic inflammatory processes, achieving resolution of symptoms in up to 90% of cases at 30 to 45 days after treatment. Based on the good results obtained, we decided to prescribe PRP for this patient. Two PRP interventions were scheduled at an interval of 2 weeks. The PRP was obtained by taking 20 mL of peripheral anticoagulated blood (sodium citrate 3.8 %; 9:1 blood:anticoagulant) and processing it using the closed and disposable PRP system Cutaneous (Proteal, Barcelona, Spain). After differential centrifugation (1800 rpm - 8 minutes), 2 plasmatic fractions were obtained: the PPP (platelet poor plasma) from the upper plasma phase and the PRP from the lower one, corresponding to the last 4 mL before reaching the buffy coat. Once reverted, the PRP was activated with $CaCl_2$ 10% (0.05 activator:1 plasma). After administration of a local anesthetic cream (lidocaine/prilocaine 5 %), activated PRP was injected intradermally using a 27 G syringe in the region of the erythematous halo characteristic of the disease, administering 2 mL on each side of the vulva vestibule. In addition, the PPP obtained during the plasma fraction separation (6 mL) was also injected intradermally in both labia majora (3 mL in each labia). After administration, the patient was advised not to take nonsteroidal anti-inflammatory drugs for 2 weeks as this could impair platelet function.[2]

A visual analog scale was used to assess the subjective variations clinical symptoms (see Table 1). There was a significant reduction of symptoms evaluated at 15 and 30 days after the first treatment with PRP for all symptoms. Thirty days after the first PRP application, clinical evaluation of erythema, purpuric rashes, erosions, and vaginal dryness showed a considerable reduction of all physical examination findings. The patient was assessed again at 6 months and showed almost complete resolution of clinical symptoms with an important reduction of the evident lesion on the left labia minora (see Figure 3). The patient provided her consent to publish this case report as well as the images contained in this report.

DISCUSSION

There is no known or documented information on the use of PRP as a treatment for Zoon vulvitis. Several treatments for the complaint have been reported in the literature with unpredictable rates of success.[3] Examples of these treatments are topical and intralesional corticosteroids, misoprostol, immunosuppressive agents such as imiquimod or calcineurin inhibitors (i.e., tacrolimus), interferon alpha, and, in very recalcitrant cases, surgical resection.[4,5]

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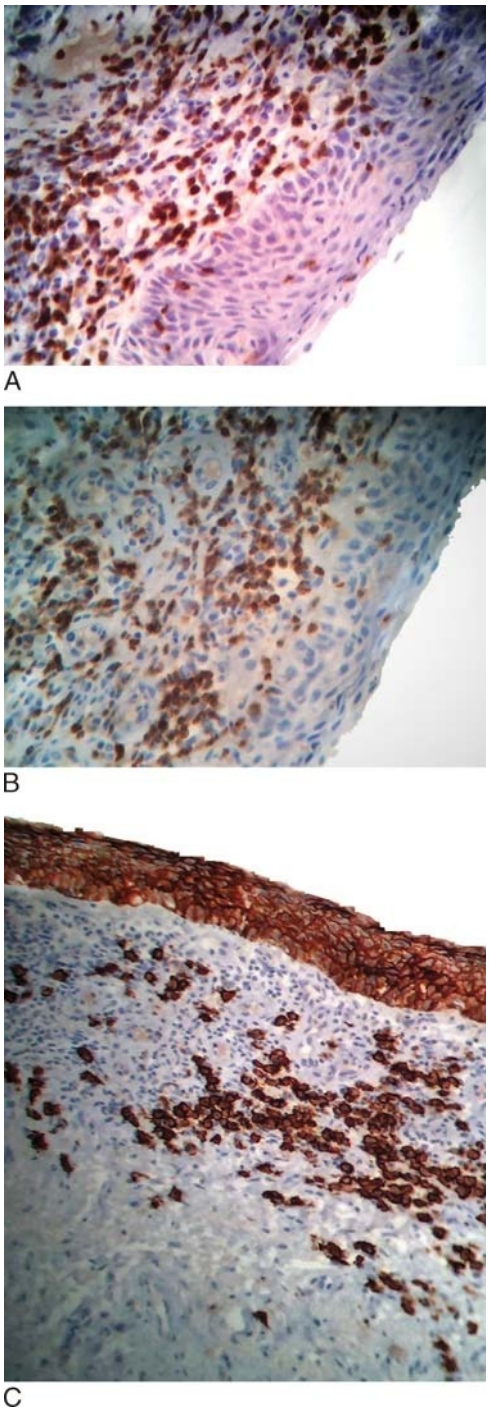

FIGURE 1. Zoon vulvitis histopathological examination before treatment shows a epidermal thinning, presence of distinctive lozenge-shaped keratinocytes with sparse dyskeratosis and spongiosis, and a dense inflammatory infiltrate of (A) T-lymphocytes (CD3+), (B) B-Lymphocytes (CD20+), and (C) plasma cells (CD138+) being more remarkably in the upper dermis. Immunohistochemical staining, original magnification, ×400 (A, B) and ×200 (C).

Sometimes, symptoms may resolve while the lesions continue to persist. Platelets play a fundamental role in hemostasis and are a natural source of growth factors and other signaling molecules with biological properties. Once platelets are activated by a variety of substances or stimuli, such as thrombin, calcium chloride, or collagen proteins,

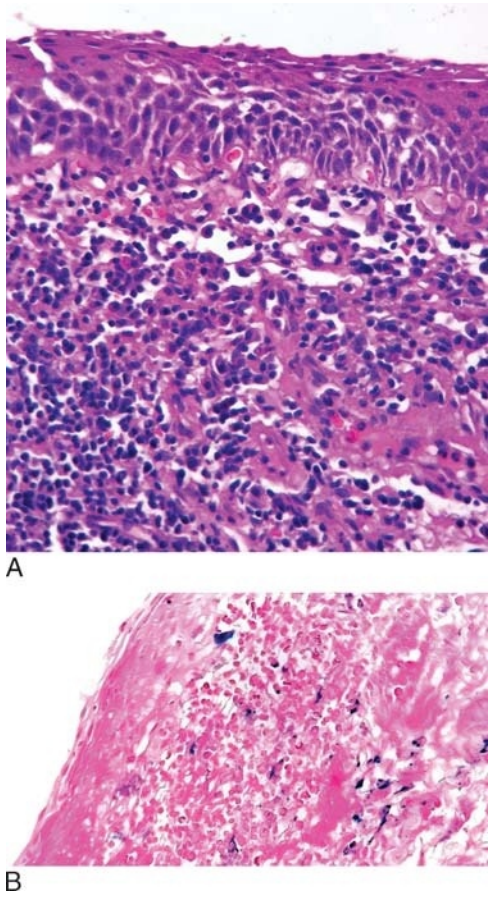

FIGURE 2. Zoon vulvitis histopathological examination before treatment. A, Hematoxilin-eosin staining, original magnification ×400. B, Perl prussian blue staining technique for hemosiderin deposits, original magnification ×200.

the bioactive substances contained in alpha and dense granules are released triggering a paracrine effect in the injured or damaged tissue, stimulating wound healing and regenerative processes.[6] Other effects associated to platelet activation include chemotaxis,[7] angiogenesis,[8] and cell proliferation and differentiation.[9] Growth factors released by the platelets in PRP, such as platelet-derived growth factor, insulin-like growth factor, vascular endothelial growth factor, platelet-derived angiogenic factor, and transforming growth factor beta, might be responsible, at least in part, for the local anti-inflammatory effects of PRP.[10] In addition, PRP may induce the

TABLE 1. Visual analogue scale used to assess the subjective variations of pruritus, burning, soreness, and dyspareunia

		After PRP treatment		
Symptom	**Before PRP treatment**	**Day 15**	**Day 30**	**6 mo**
Pruritus	9	5	3	1
Burning	8	4	2	0
Soreness	8	4	2	0
Dyspareunia	9	6	5	1

PRP indicates platelet-rich plasma.

The scale assigned a value of 10 to the highest intensity of each symptom and value of 0 to their absence.

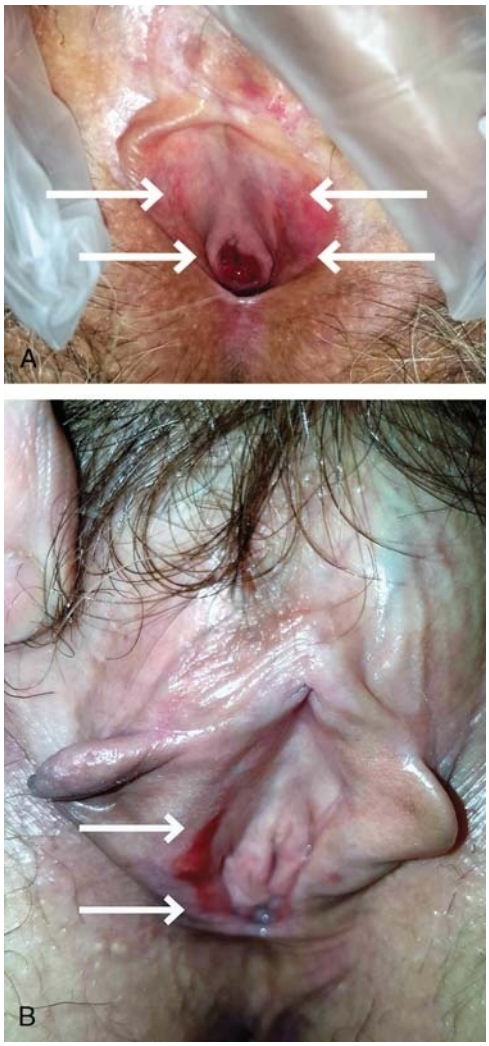

FIGURE 3. A, Macroscopic appearance of Zoon vulvitis before PRP treatment: atrophic pale mucosa and a u-shaped bright erythema in vulvar introitus. B, Dermatological examination of the vulva after PRP treatment at 6 months, showing a reduction of the erythematous halo, a more vascularized vulva without dryness, and the presence of mucus. Triangles demarcate the margin of the lesion.

cell production of endocannabinoid cells under inflammatory conditions, thus explaining its analgesic effects.[11] Stimulation of cell surface toll-like receptors by chemokines and cytokines can trigger inflammation by activation of nuclear factor κB (NF-κB), an essential and ubiquitous transcription factor that mediates inflammatory and catabolic events. In addition, the role of the NF-κB signaling system has been described in both maturing and B-cell proliferation through specific receptors.[12,13] In this sense, the growth factors released by platelets could inhibit the expression and assembly of NF-kB and consequently might aid in suppressing inflammation by repressing genes associated with the production of pro-inflammatory cytokines such as cyclooxygenase 2 and the expression of chemokine receptors–like CXCR4 (which promote the chemotaxis of monocyte-like cells).[14] In addition, because of the low expression of NF-kB, there would be a negative modulation of the proliferation and maturation of plasma cells, leading to overall control of local inflammation. Moreover, immunohistochemical investigations of the dermal infiltrate have revealed the presence of immunoglobulins (IgA, IgE, IgG), probably produced by plasma cells, that could trigger an inflammatory reaction due to hypersensitivity in the area of the lesion.[15] We suggest that immunomodulation of plasma cells by PRP might also affect Ig secretion and diminish progress of the disease. Even when the clinical symptoms in this patient improved significantly, the area of involvement was not cleared to the same degree. Other reports have described the same phenomena. We believe that this is due to the presence of hemosiderin deposits. Purpuric lesions are the result of the extravasation of red cells from the vasculature into the skin and/or subcutaneous tissue. Once in the tissue, the hemosiderin complex forms within cells (mainly macrophages) and causes hyperpigmentation. Iron pigments are typically resolved with time, but sometimes, it may take a long time (even years) for the body to metabolize them.[3,16,17] Clinically, the patient presented whitish areas with mucosal atrophy and erythematous areas, specifically on the lower lips. The skin biopsy corresponded to the lower lip mucosa, where the erythematous area was more evident. The clinical response observed after PRP treatment was in the erythematous areas, where the symptoms improved significantly. Whitish areas were not biopsied. On the basis of the clinical and histological results, we considered the possibility that the patient was developing areas of Zoon vulvitis (histologically confirmed) over a nonhistologically confirmed lichen sclerosus and atrophic. In addition, we do not discard the possibility that the patient had a clinical Zoon vulvitis "lichen sclerosus like." Further studies including more patients are needed to confirm the beneficial effect of PRP in the pathogenesis of PLC.

REFERENCES

1. Salopek TG, Siminoski K. Vulvitis circumscripta plasmacellularis (Zoon's vulvitis) associated with autoimmune polyglandular endocrine failure. *Br J Dermatol* 1996;135:991–4.
2. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol* 1995;35: 209–19.
3. Botros SM, Dieterich M, Sand PK, et al. Successful treatment of Zoon's vulvitis with high potency topical steroid. *Int Urogynecol J Pelvic Floor Dysfunct* 2006;17:178–9.
4. Goldstein AT, Christopher K, Burrows LJ. Plasma cell vulvitis: a rare cause of intractable vulvar pruritus. *Arch Dermatol* 2005;141:789–90.
5. Gurumurthy M, Cairns M, Cruickshank M. Case series of Zoon vulvitis. *J Low Genit Tract Dis* 2010;14:56–8.
6. Xian LJ, Chowdhury SR, Bin Saim A, et al. Concentration-dependent effect of platelet-rich plasma on keratinocyte and fibroblast wound healing. *Cytotherapy* 2015;17:293–300.
7. Casati L, Celotti F, Negri-Cesi P, et al. Platelet derived growth factor (PDGF) contained in platelet rich plasma (PRP) stimulates migration of osteoblasts by reorganizing actin cytoskeleton. *Cell Adh Migr* 2014;8:595–602.
8. Kakudo N, Morimoto N, Ogawa T, et al. Angiogenic effect of platelet-rich plasma combined with gelatin hydrogel granules injected into murine subcutis. *J Tissue Eng Regen Med* 2015;11:1941–8.
9. Mishra A, Tummala P, King A, et al. Buffered platelet-rich plasma enhances mesenchymal stem cell proliferation and chondrogenic differentiation. *Tissue Eng Part C Methods* 2009;15:431–5.
10. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol* 2013;12:721–30.
11. Descalzi F, Ulivi V, Cancedda R, et al. Platelet-rich plasma exerts antinociceptive activity by a peripheral endocannabinoid-related mechanism. *Tissue Eng Part A* 2013;19:2120–9.

12. Almaden JV, Tsui R, Liu YC, et al. A pathway switch directs BAFF signaling to distinct NFκB transcription factors in maturing and proliferating B cells. *Cell Rep* 2014;9:2098–111.
13. De Silva NS, Silva K, Anderson MM, et al. Impairment of mature B Cell maintenance upon combined deletion of the alternative NF-κB transcription factors RELB and NF-κB2 in B cells. *J Immunol* 2016;196: 2591–601.
14. Bendinelli P, Matteucci E, Dogliotti G, et al. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-κB inhibition via HGF. *J Cell Physiol* 2010;225:757–66.
15. Kuniyuki S, Asada T, Yasumoto R. A case of vulvitis circumscripta plasmacellularis positive for herpes simplex type II antigen. *Clin Exp Dermatol* 1998;5:230–31.
16. Fujimura T, Furudate S, Ishibashi M, et al. Successful treatment of plasmacytosis circumorificialis with topical tacrolimus: two case reports and an immunohistochemical study. *Case Rep Dermatol* 2013;5: 79–83.
17. Virgili A, Mantovani L, Lauriola MM, et al. Tacrolimus 0.1% ointment: is it really effective in plasma cell vulvitis? Report of four cases. *Dermatology* 2008;216:243–6.