Treatment of Primary Vulvar Paget Disease With 5% Imiquimod Cream

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Introduction: Our objective was to evaluate the efficacy of conservative treatment with imiquimod in Paget vulvar disease.

Materials and Methods: We describe a case series that includes 10 patients with histopathologic diagnosis of extramammary Paget disease of the vulva, who were treated with 5% imiquimod cream. Of these patients, 3 were treated for recurrent disease and 7 were treated for initial primary disease. The patients applied the cream every other day until the lesions were no longer clinically detected.

They were previously instructed on how and where to apply the cream by making them use a mirror while following the physician's directions.

Results: Complete clinical and histologic remission of the disease was achieved in 9 patients. The remaining patient had partial histologic response and is still under treatment. The treatment was well tolerated despite moderate irritation. No recurrences were observed during a mean follow-up of 18 months.

Conclusions: On the basis of the results, the authors consider that 5% imiquimod cream could be considered a safe and effective therapeutic option for the treatment of primary vulvar Paget disease. Further studies are needed to determine the real efficacy and safety of 5% imiquimod cream for the treatment of this infrequent disease.

Key Words: extramammary Paget disease, imiquimod, topical chemotherapy, vulva

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Extramammary Paget disease is an intraepithelial adenocarcinoma arising in the apocrine glands of the skin. It accounts for 1% to 2% of vulvar cancers.[1,2]

Surgical resection with wide safety margins (1.5–2 cm) represents the conventional treatment.[3] However, even after achieving negative margins, recurrence rates are high, ranging from 20% to 60%.[4]

Because this treatment alters the normal vulvar anatomy and function, more conservative treatments are being investigated. Recently, 5% imiquimod cream has been suggested as an alternative for the initial management of the primary disease as well as for recurrences. It is considered a safe and effective treatment.[5]

MATERIALS AND METHODS

We describe a case series that includes 10 women with histologic diagnosis of extramammary Paget disease of the vulva, who were selected for clinical treatment; of them, 3 were treated for recurrent disease and 7 were treated for initial primary disease. All the patients had immunohistochemistry that confirmed primary vulvar Paget disease.

Approval of the ethics committee of the Hospital Italiano, Buenos Aires, was obtained to conduct this observational and prospective study, taking into account that this is an off-label use of 5% imiquimod cream.

The patients included in this study had declined surgery and signed an informed consent where it was stated that this therapy is not guaranteed to treat extramammary Paget disease.

All suspicious lesions such as ulcers, nodules, or indurated areas were sampled by biopsy and submitted for histopathologic examination to rule out invasive disease or underlying adenocarcinoma. Skin, gynecologic, and breast examinations were carried out, as well as a urological evaluation in patients with periurethral lesions (including cystoscopy) and a coloproctologic evaluation in patients with perianal lesions (by performing a colonoscopy).

The patients applied 5% imiquimod cream on the lesions and up to 2 cm outside their visible margins every other day. They were previously instructed on how and where to apply the cream by making them use a mirror while following the physician's directions.

Monthly checkups were scheduled after starting the treatment until the clinical disappearance of the disease. Histologic examination of the treated area was carried out 2 months after having finished the treatment to avoid diagnostic difficulties associated with the inflammatory response generated by imiquimod.

Three of the patients, aged 63, 64, and 60 years old, respectively, had recurrent Paget disease of the vulva after several surgical treatments. Clinical disappearance of the disease was observed 4 months after starting treatment, and biopsies of the treated area were negative for Paget disease in all 3 patients. Currently, they all remain disease free, with a follow-up of 42, 31, and 49 months, respectively (see Table 1).

The 7 remaining patients, aged between 60 and 92 years old, had initial primary Paget disease of the vulva. The 92-year-old patient (see Figure 6) presented an indurated, raised lesion on the left labium majus, which was resected, thus ruling out invasive disease and underlying adenocarcinoma. All 7 patients were treated with 5% imiquimod cream, as explained above, until clinical disappearance of the disease. Six patients showed a complete response, with negative biopsies for Paget disease. The 92-year-old patient showed partial response and is still under treatment. Length of treatment varied from 5 to 7 months, and the follow-up ranged between 3 and 5 months for this group (see Table 1; patients 4 to 10).

RESULTS

Complete clinical and histologic remission of the disease was achieved in 9 patients. The remaining patient, who belonged to the group of patients with initial primary Paget disease, had a partial histologic response and is still under treatment (see Table 1).

Only local adverse effects were observed in the study group, which were moderate local irritation and some erosion, both of which were well tolerated by patients.

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TABLE 1. Summary of Hospital Italiano de Buenos Aires Data of Patients With Extramammary Paget Disease Under Imiquimod Therapy

Case no.	Disease	Treatment length (mo)	Outcome	Follow-up (mo)
1	Recurrent	4	Clinical and histologic remission	42 mo; ongoing
2	Recurrent	4	Clinical and histologic remission	31 mo; ongoing
3	Recurrent	4	Clinical and histologic remission	49 mo; ongoing
4	Initial	5	Clinical and histologic remission	18 mo; ongoing
5	Initial	6	Clinical and histologic remission	3 mo; ongoing
6	Initial	5	Clinical and histologic remission	3 mo; ongoing
7	Initial	5	Clinical remission, histologic persistence	2 mo; ongoing
		7	Clinical and histologic remission	
8	Initial	4	Clinical and histologic remission	15 mo; ongoing
9	Initial	6	Clinical and histologic remission	2 mo; ongoing
10	Initial	5	Clinical persistence	Under treatment

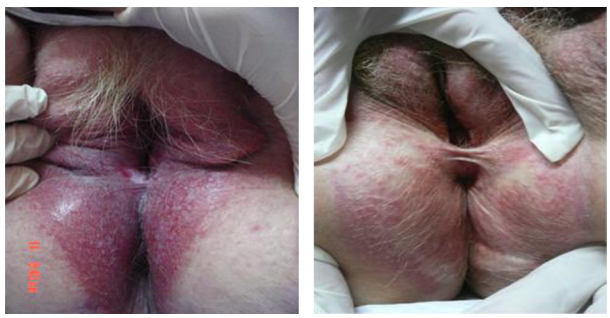

FIGURE 1. Patient 1: clinical evaluation before and after treatment with imiquimod.

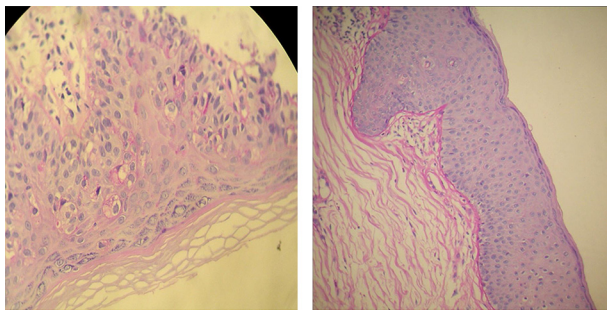

FIGURE 2. Patient 1: histopathology before and after medical treatment with 5% imiquimod cream.

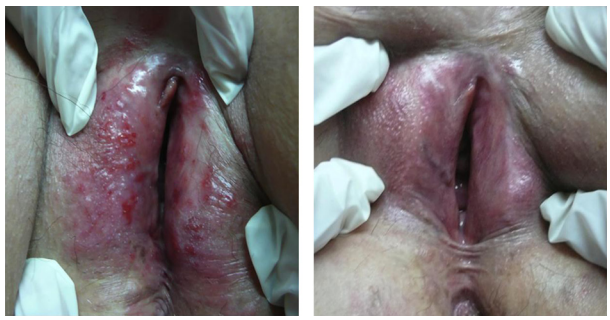

FIGURE 3. Patient 2: clinical evaluation before and after treatment with imiquimod.

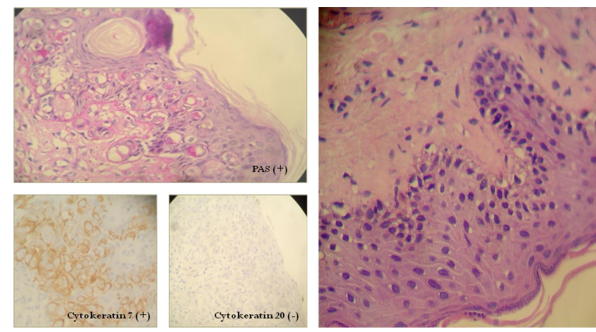

FIGURE 4. Patient 2: histopathology before and after medical treatment with 5% imiquimod cream.

No recurrences were observed during a mean follow-up of 18 months (see Figures 1–6).

DISCUSSION

Several treatments, each with variable effectiveness, are available to treat the disease, namely laser surgery, aminolevulinic acid photodynamic therapy, radiotherapy, topical chemotherapy, and wide surgical excision. Although surgery is generally accepted as the standard form of treatment, all surgical procedures, including extensive resections, are associated with high rates of recurrence (20%–60%).[4] Therefore, there has been a shift toward a more conservative approach; thus, the treatment that offers both a low recurrence rate and minimal tissue destruction is considered

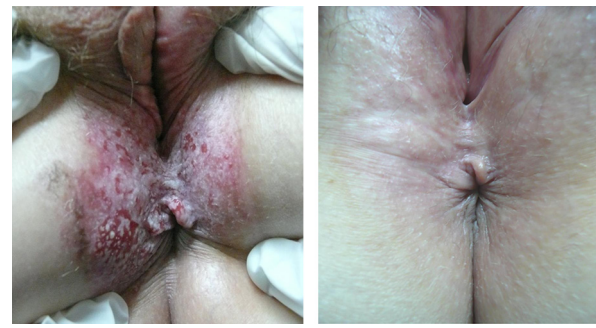

FIGURE 5. Patient 4: clinical evaluation before and after treatment with imiquimod.

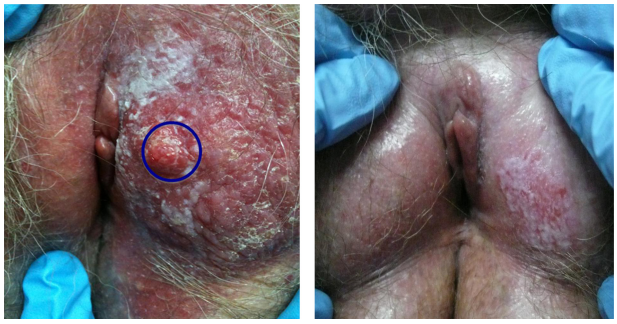

FIGURE 6. Patient 10: clinical evaluation before and after 5 months of treatment with 5% imiquimod cream. An erythematosquamous lesion involving the labia minora and majora and the perineal skin. In addition, an indurated and raised area was evident. The biopsy confirmed primary vulvar Paget disease and ruled out stromal invasion and adnexal carcinoma. Clinical and histologic evaluation after 5 months of treatment with imiquimod showed disease persistence.

to be the ideal one. A topical immunomodulator that induces cytokine production and stimulates the innate and cellular immune response (imiquimod cream) has recently been used for the treatment of primary or recurrent Extramammary Paget disease, showing complete eradication, without recurrence.[6,7] Imiquimod is an immune response modifier that stimulates the production of a wide range of cytokines, interferon-α and tumor necrosis factor-α. Being an agonist of toll-like receptors, it leads to the combined activation of innate local immunity and T_H1 immune response as well as to the inhibition of T_H2 cytokines, which are overexpressed in skin cancer. Imiquimod may also have direct antineoplastic activity, encouraging migration of Langerhans cells, inducing apoptosis, and inhibiting tumor-associated angiogenesis. However, the mechanism of action by which imiquimod promotes tumor eradication in extramammary Paget disease remains to be determined.[8]

Topical therapy with imiquimod cream is suggested as a safe and effective treatment option for this condition.[9–14] Since imiquimod was first described to treat primary vulvar extramammary Paget disease by Wang et al. in 2003,[7] 29 additional cases have been documented with variable outcomes (see Table 2). Of all the primary disease cases (n = 12), 50% have achieved clinical resolution with imiquimod therapy alone. Of the recurrent primary disease cases (n = 15), 73% have achieved clinical resolution with imiquimod therapy alone.

TABLE 2. Summary of Literature Findings for Imiquimod Therapy on Extramammary Paget Disease of the Vulva

Author	Type of article	Disease	Treatment length (wk)	Outcome	Follow-up
Wang et al. (2003)[7]	Case report (n = 1)	Recurrent	7	Clinical and histologic remission	2 wk
Denehy et al. (2008)[6]	Abstract (n = 6)	Recurrent	6–16	Complete remission: 5	6 mo
				Partial remission: 1	
Geisler et al. (2008)[9]	Case report (n = 1)	Recurrent	16	Clinical and histologic remission	12 mo
Gass et al. (2008)[16]	Abstract (n = 2)	Unknown	16	Partial response	—
Hatch and Davis (2008)[4]	Case series (n = 2)	Recurrent	12/21	Clinical and histologic remission	4 and 7 mo
Challenor et al. (2009)[17]	Case series (n = 2)	Initial	12	Clinical remission	3 and 4 mo
Sendagorta et al. (2010)[5]	Case series (n = 3)	Initial	6	Clinical and histologic remission	26 mo
Ho et al. (2010)[18]	Case report (n = 1)	Initial	18	Clinical improvement, lost to follow-up	—
Tongue et al. (2011)[19]	Case report (n = 1)	Recurrent	17	Clinical and histologic remission	24 mo
Baiocchi et al. (2012)[20]	Case series (n = 4)	Initial (n = 1)	4	Residual disease (vulvectomy; positive margins)	21 mo
		Recurrent (n = 3)	50+	Clinical improvement	—
			20	75% clearance, developed EMPD vagina	40 mo
			52	Clinical and histologic remission; recurrence 17 wk later	
Sanderson et al. (2013)[15]	Case series (n = 6)	Initial (n = 5)	14	Clinical remission	18 mo
			16	Residual disease; discharged with stable disease	—
			16	Clinical remission; recurrence 18 mo later	24 mo
			8	Clinical remission	18 mo
			16	Clinical improvement	12 mo
		Recurrent (n = 1)	16	Clinical improvement; excision requested	Awaiting first follow-up

CONCLUSIONS

Topical imiquimod was an effective treatment both for recurrent and for initial primary vulvar Paget disease in 9 of the 10 patients presented herein. It proved to be a safe and effective option for the treatment of vulvar Paget disease, especially in those patients with extensive lesions or those at high risk for surgical treatment because of comorbidities. Surgical excision or an alternative therapeutic option can be reserved for those patients whose extramammary Paget disease persists or recurs after topical treatment with imiquimod. However, it should be kept in mind that because of the low prevalence of the disease, the small number of cases reported in different series, and the poor long-term follow-up, it is difficult to determine the real effectiveness of topical imiquimod therapy. Moreover, the number of cases published is too limited to allow generalizations. Obviously, the promising results obtained must be validated with clinical trials, which should evaluate not only the efficacy and safety of the treatment but also the most appropriate treatment course. Therefore, treatment with topical imiquimod is still considered to be a very promising therapy for this rare disease.

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