Topical Imiquimod Therapy for Basal and Squamous Cell Carcinomas: A Clinical Experience

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Basal cell carcinomas (BCCs) and cutaneous squamous cell carcinomas (SCCs) are the most common malignancies in humans. Together, they constitute approximately 95% of nonmelanoma skin cancers (NMSCs). Surgical excision remains the mainstay of therapy of low-risk NMSC, though Mohs micrographic surgery is the gold standard for high-risk NMSC. Both methods produce high cure rates, but they may not be appropriate treatments for elderly patients who are either not surgical candidates or refuse to undergo surgery for their skin cancers. Imiquimod cream 5% is a topical immune response modifier that targets the toll-like receptors 7 and 8 and up-regulates inflammatory pathways targeting diseased tissue. This noninvasive topical therapy may be more appropriate for some patients. Herein, we describe our 5-month clinical experience in mostly elderly subjects with BCC (n=21) or SCC (n=19) who were not candidates for surgical excision and were treated with topical imiquimod. Most subjects had a history of skin cancer, and the median age of the subjects was 78 years and 79 years in the BCC and SCC groups, respectively. After biopsy alone or biopsy followed by curettage, subjects received imiquimod cream 5% once daily 5 times weekly for 6 weeks. Twenty-three BCC lesions and 22 SCC lesions were included in the analysis. Most of the 45 lesions treated were located on the head and most were in high-risk areas. Approximately 3 months after imiquimod therapy, repeat biopsies showed that only 3 (2 BCCs and 1 SCC) lesion sites had residual tumor. After a median follow-up of 26 months, there was only one additional SCC recurrence.

We also present a selection of representative case studies. Imiquimod cream 5% as adjunctive therapy to curettage was safe and well-tolerated in this mostly elderly population. The improved residual tumor and recurrence rates compared with historical rates for electrodesiccation and curettage (ED&C) alone suggest that adjunctive imiquimod therapy may be an appropriate treatment option for patients who desire or require less invasive treatment for NMSCs.

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Nonmelanoma skin cancers (NMSCs), which primarily consist of basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), are the most common malignancies occurring in humans. It is estimated that in 2004 there were more than 1 million new cases of BCC and 200,000 new cases of SCC in the United States.[1] However, the true incidence of BCC and SCC is unknown. The estimated number of NMSC cases is likely to be understated because they are not documented by the National Cancer Institute or most state registries. Furthermore, in the last several decades, the incidence of BCC has increased by an estimated 20% to 80%, and the incidence of SCC has increased by an estimated 3% to 10%.[2]

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Table 1.

Demographics of Subjects With Basal Cell Carcinoma

Characteristic	Subjects (n=21)
Sex, n (%)	
Male	14 (67)
Female	7 (33)
Median age, y (range)	78 (39–95)
Median follow-up, mo (range)	26 (5–34)
Prior history of skin cancer, n (%)	13 (62)*
Basal cell carcinoma	10 (48)
Squamous cell carcinoma	3 (14)
Unspecified skin cancer	3 (14)
Melanoma	0 (0)

*Three subjects had both basal and squamous cell carcinomas.

Table 2.

Baseline Lesion Characteristics for Subjects With Basal Cell Carcinoma*

Characteristic	Lesions (n=23)
Type of BCC, n (%)	
Unspecified†	16 (70)
Infiltrative	5 (22)
Nodular infiltrative	1 (4)
Recurrent infiltrative	1 (4)
Location, n (%)	
Nose	7 (30)
Temple	6 (26)
Forehead	2 (9)
Limbs/Extremities	2 (9)
Lip	2 (9)
Cheek	1 (4)
Eyebrow	1 (4)
Neck	1 (4)
Postauricular	1 (4)
Median size, cm (range)	1.2 (0.4–1.9)

*BCC indicates basal cell carcinoma.
†This type of BCC did not conform completely to the commonly recognized types of BCC.

Development of both BCC and SCC are reportedly related to chronic UV light exposure. Not surprisingly, areas of the skin frequently exposed to the sun, such as the face, ears, forehead, and neck, have the highest incidence of these malignancies. Nonetheless, some NMSCs occur on areas of the skin not exposed to the sun.[3] Men and elderly patients have a higher incidence of BCCs and SCCs than women or younger patients, presumably because they have more exposure to UV light. Unfortunately, elderly patients often refuse, do not receive, or cannot tolerate prescribed therapies.

Standard treatment strategies for patients with NMSC include surgical excision, Mohs micrographic surgery, and electrodesiccation and curettage (ED&C). Other options available are radiation therapy, cryotherapy, and other topical therapies. Surgical excision is considered the gold standard for treating BCC and SCC because it offers histologic margin control; however, healthy tissue is removed, and there is potential for surgical complications and scarring. To preserve tissue and improve histologic margin control on high-risk BCCs and SCCs, Mohs micrographic surgery often is used. This procedure has the highest cure rate and provides improved tissue conservation versus surgical excision.[4] However, Mohs micrographic surgery requires specialized training, is time consuming, and is not always readily available. ED&C is the most common treatment strategy used by dermatologists to treat BCCs and SCCs and is the least invasive surgical procedure. However, residual tumor is present immediately after ED&C in approximately 20% to 40% of cases.[5,6] This technique has no specific margin control and is associated with lower cure rates, especially with larger lesions, compared with surgical excision and Mohs micrographic surgery.

Despite the widespread use of surgical techniques in the treatment of NMSCs, these treatment strategies may not be appropriate for all patients. Patients with cosmetic concerns or those with lesions in highly visible areas may not want to undergo a surgical procedure. Moreover, elderly patients may not want or be able to tolerate these invasive techniques because of quality-of-life concerns. Because inappropriate management of these malignancies can cause morbidity and mortality, improved treatment strategies are needed.

Imiquimod cream 5% is a topical immune response modifier that is approved for the treatment of external genital and perianal warts in individuals 12 years and older, actinic keratoses on the face or scalp in immunocompetent adults, and

Table 3.

Demographics of Subjects With Squamous Cell Carcinoma

Characteristic	Subjects (n=19)
Sex, n (%)	
Male	10 (53)
Female	9 (47)
Median age, y (range)	79 (67–98)
Median follow-up, mo (range)	27 (3–35)
Prior history of skin cancer, n (%)	14 (74)*
Squamous cell carcinoma	10 (53)
Basal cell carcinoma	6 (32)
Unspecified skin cancer	4 (21)
Melanoma	0 (0)

*Six subjects had both squamous and basal cell carcinomas.

Table 4.

Baseline Lesion Characteristics for Subjects With Squamous Cell Carcinoma*

Characteristic	Lesions (n=22)
Type of SCC, n (%)	
Intraepithelial	13 (59)
Superficial and well-differentiated	6 (27)
ImdSCC	1 (5)
MwdSCC	2 (9)
Location, n (%)	
Cheek	5 (23)
Ear	4 (18)
Forehead	4 (18)
Nose	3 (14)
Lip	2 (9)
Neck	2 (9)
Scalp	2 (9)
Median size, cm (range)	1.1 (0.5–1.8)

*SCC indicates squamous cell carcinoma; ImdSCC, intraepithelial moderately differentiated SCC; MwdSCC, moderately well-differentiated SCC.

superficial BCCs on the trunk in immunocompetent adults. In addition, imiquimod also is being investigated in the treatment of SCC.[7,8] This toll-like receptor 7/8 agonist is a potent stimulator of the innate and cell-mediated immune responses.[9,10] The antitumor and immunoregulatory properties of imiquimod are mediated by cytokine production by peripheral blood mononuclear cells.[11] This inflammatory cytokine profile is associated with a local inflammatory response at the treatment site and is generally very well-tolerated with minimal side effects. Therefore, compared with the surgical treatment options for BCC and SCC, imiquimod is a noninvasive therapeutic approach.

The purpose of the current study was to document a 5-month clinical experience and investigate the effectiveness of topical imiquimod therapy following curettage in subjects with BCC or SCC who did not want or could not tolerate more invasive surgical treatment.

Methods

Participants—Individuals 18 years and older with histologically confirmed BCC or SCC and a first biopsy conducted between February 1, 2003, and June 30, 2003, were eligible. Individuals who refused surgical treatment or could not tolerate surgery because of advanced age, comorbidity, or the inability to travel were included in the analysis. Eligible individuals also were required to have a repeat biopsy after imiquimod therapy and a repeat biopsy of any suspicious lesions during the follow-up period.

Treatment and Assessment—Lesions were measured and then a biopsy was performed. Some lesions were treated with imiquimod alone, and others were treated with curettage after biopsy to debulk any residual tumor using a No. 1 or 2 curette. Electrodesiccation only was used to control bleeding. Seven to 14 days after biopsy alone or after curettage following biopsy, subjects applied topical imiquimod cream 5% once daily 5 times weekly for 6 weeks. Because skin reactions were expected, rest periods were allowed as needed. However, rest periods did not extend the treatment period. Biopsies of the lesion sites were performed again 3 months after treatment. In most cases, the entire scar was removed in a shave fashion. Skin reactions to imiquimod therapy and tumor recurrence up to 34 months posttreatment were assessed.

Results

Twenty-one subjects with 23 BCCs were included in the analysis (Table 1). Most subjects were men, with a median age of 78 years. Most subjects (13/21; 62%) had a history of skin cancer, including 10 subjects (48%) with a prior history of BCC. Sixteen lesions (70%) were unspecified BCC and

Table 5.

Treatment and Skin Reaction to Imiquimod Therapy by Lesion Type*

	BCC Lesions (n=23)	SCC Lesions (n=22)
Surgery, n (%)		
Shave biopsy alone	5 (22)	2 (9)
Curettage after biopsy	18 (78)	20 (91)
Imiquimod therapy		
Number of applications, median (range)	22 (10–62)	20 (8–30)
Median duration of therapy, wk (range)	6 (5.5–7.5)	6 (3.5–7)
Local skin reactions to imiquimod therapy, n (%)		
Mild	7 (30)	14 (64)
Moderate	8 (35)	5 (23)
Significant	8 (35)	3 (14)

*BCC indicates basal cell carcinoma; SCC, squamous cell carcinoma.

7 lesions (30%) were infiltrative BCC. Twenty lesions were located on the head, mostly in high-risk areas (ie, ear, nose, forehead). In addition, the lesions were large, with a median size of 1.2 cm (Table 2).

Nineteen subjects with 22 SCCs were included in the analysis (Table 3). Approximately half of the subjects were men, and most subjects (14/19; 74%) had a prior history of skin cancer; 10 subjects (53%) with a prior history of SCC. The median age of these subjects was 79 years. Most SCCs (13 lesions [59%]) were intraepithelial SCCs (Table 4). Six lesions (27%) were superficial and well-differentiated. Similar to the subjects with BCC, subjects with SCC included in this study also had large and/or high-risk lesions. The median size was 1.1 cm, and most lesions were located in high-risk areas.

Thirty-eight of 45 BCC and SCC lesions (84%) were debulked by curettage after biopsy (Table 5). Seven lesions were treated by shave biopsy alone. Subjects with BCC lesions received a median of 22 applications of imiquimod for a median duration of 6 weeks of therapy. Similarly, subjects with SCC lesions received a median of 20 applications of imiquimod for a median duration of 6 weeks of therapy. Most subjects had mild to moderate skin reactions to topical imiquimod. Eight subjects with BCC lesions and 3 subjects with SCC lesions had skin reactions classified as significant.

Three to 11 weeks after the completion of imiquimod therapy, repeat biopsies were performed of lesion sites and assessed for the presence of residual tumor. Of the 23 BCC lesion sites reevaluated, 2 (9%) had residual tumor. One subject with residual BCC received 6 additional weeks of imiquimod therapy using the same regimen, and one subject with residual BCC underwent Mohs micrographic surgery. Of the 22 SCC lesion sites reevaluated, 1 (5%) had residual tumor after imiquimod therapy. The subject was referred for radiation therapy. With a median follow-up of 26 months for subjects with BCC lesions and 27 months for subjects with SCC lesions, only one subject in the SCC group experienced a recurrence. Except for skin reactions, none of the subjects reported any adverse events, including pain at the application site, while receiving imiquimod therapy. Some subjects required a rest period.

BCC Case Studies—A representative photograph of a subject with a BCC lesion on the eyebrow that responded to 6 weeks of imiquimod therapy is provided in Figure 1. This 92-year-old woman with a history of 5 prior BCC lesions presented with a 1.4-cm infiltrative recurrent BCC lesion. Fourteen days after curettage, she received 40 total applications of imiquimod in 6 weeks. This subject experienced a skin reaction to imiquimod that was classified as significant. Six weeks after imiquimod therapy was completed, a repeat biopsy of the lesion revealed no residual tumor. After approximately 31 months of follow-up, there was no sign of recurrence, and the subject had an excellent cosmetic result.

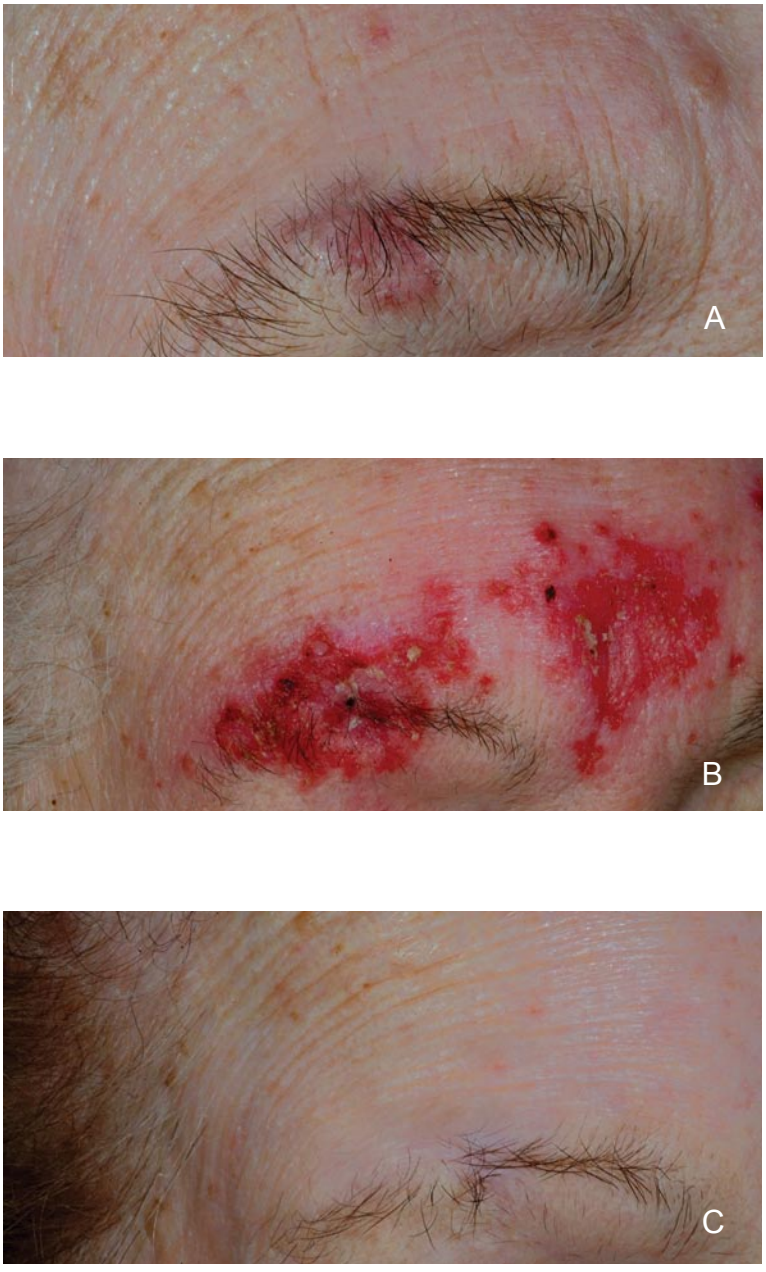

Figure 1. A 92-year-old woman with an infiltrative recurrent basal cell carcinoma lesion on the eyebrow before treatment (A) and after curettage and 6 weeks of therapy with imiquimod cream 5% (40 total applications)(B). There was no sign of recurrence after 31 months of follow-up (C).

Furthermore, this subject had a BCC lesion on the mid forehead that also responded completely to imiquimod therapy.

Results of a repeat biopsy in an 83-year-old man who presented with a BCC lesion on the fourth finger of his right hand showed residual tumor. He had a history of 12 prior BCC lesions and one prior SCC lesion. Fifteen days after curettage, the man received 28 total applications of imiquimod in 6.5 weeks. He had a very mild skin reaction to imiquimod, and 7 weeks after imiquimod therapy was completed, results of a repeat biopsy of the lesion revealed residual tumor. It is believed that this subject was noncompliant because he was concurrently using imiquimod for a BCC on the left side of his neck. The subject had a significant reaction at that location, and results of a biopsy of his neck showed no residual tumor. He then received an additional 6 weeks of imiquimod therapy (5 times weekly). The subject had a stronger skin reaction to the second application of imiquimod, and after approximately 26 months of follow-up, there was no sign of recurrence.

SCC Case Study—A representative photograph of a subject with an SCC lesion that responded to 7 weeks of imiquimod therapy is provided in

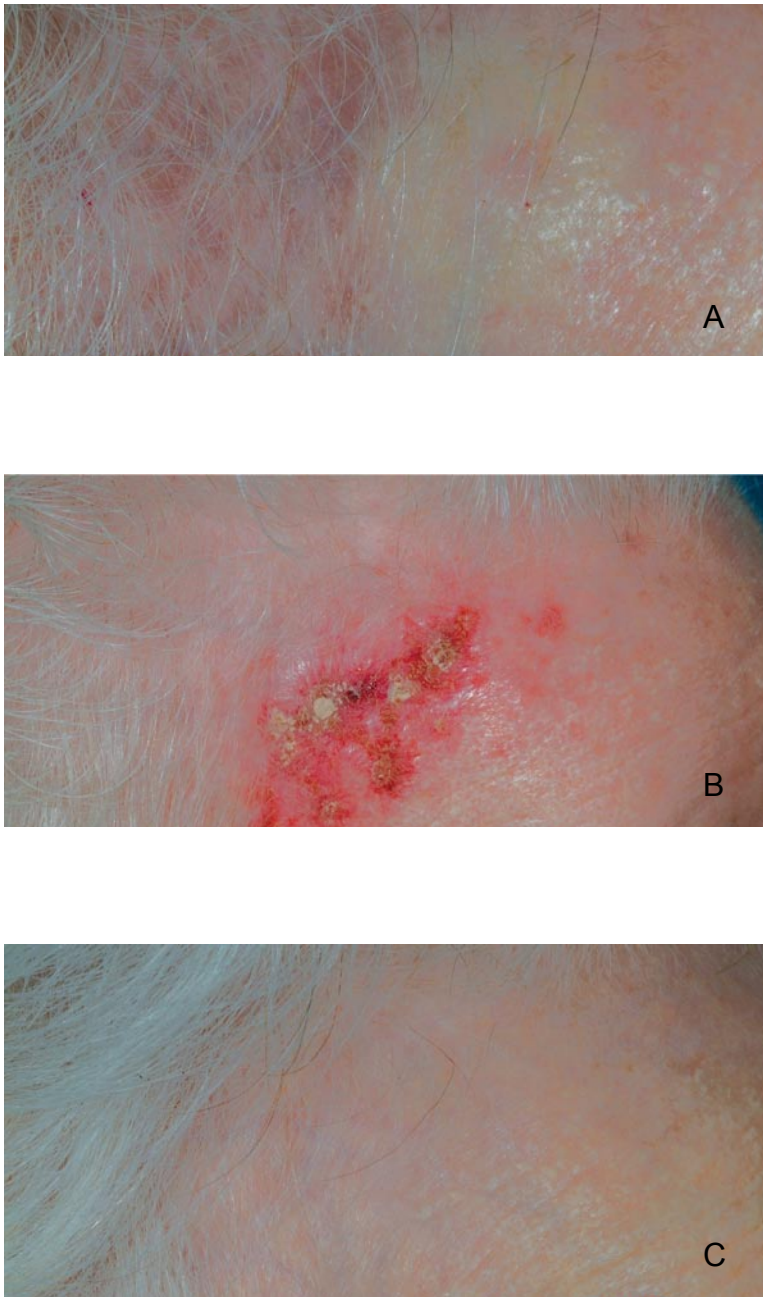

Figure 2. An 88-year-old woman with an intraepithelial squamous cell carcinoma lesion on the forehead and subclinical lesions before treatment (A) and after curettage and 7 weeks of therapy with imiquimod cream 5% (23 total applications)(B). There was no sign of recurrence after 31 months of follow-up (C).

Figure 2. This 88-year-old woman had a 1-cm intraepithelial SCC lesion on the forehead. She had a history of one prior BCC lesion. Two weeks after curettage, the subject received 23 total applications of imiquimod in 7 weeks and had a significant reaction to imiquimod therapy. Figure 2 also illustrates the treatment of subclinical lesions with imiquimod therapy. One month after treatment with imiquimod, the woman underwent a repeat biopsy; the results showed no residual tumor. After 31 months, there were no signs of recurrence.

Comment

Although BCCs rarely metastasize and 95% of SCCs are curable, if left untreated, BCCs can result in substantial morbidity and aggressive SCC lesions can lead to metastasis and even death.[12,13] Although ED&C is a common and appropriate treatment option for patients with BCC and SCC, the procedure often is associated with residual tumor, especially for lesions located on the face. It has been reported that 30% to 47% of lesions located on the head and nose that were treated with ED&C

are associated with residual tumor.[6,14,15] Residual tumor is an even greater problem for larger lesions. Spencer et al[16] reported that in BCC lesions bigger than 1 cm, ED&C failed to completely remove the tumor in up to 40% of cases. Like surgical excision and Mohs micrographic surgery, ED&C can lead to notable scarring. Although surgical excision and Mohs micrographic surgery are associated with lower rates of residual tumor than ED&C, these surgical procedures may not be appropriate for elderly patients or patients who cannot tolerate invasive procedures. Therefore, alternative treatment regimens that are less invasive yet provide improved cure rates are needed.

Minimally invasive treatment strategies, including photodynamic therapy, interferon, topical 5-fluorouracil, radiation therapy, and retinoids, have been investigated as possible treatment options for BCC and SCC, with limited success.[17] However, imiquimod has shown great promise in clinical trials, with higher clearance rates compared with placebo and low recurrence rates in the treatment of BCC and SCC.[18-23] In the current study of mostly elderly subjects, only 3 (7%) of the 45 lesions that underwent repeat biopsy were associated with residual tumor (one subject with BCC underwent an additional imiquimod treatment regimen, another subject with BCC was referred for Mohs micrographic surgery, and one subject with SCC was referred for radiation therapy). More importantly, after approximately 27 months of follow-up, only one SCC lesion recurred. The subject with the SCC recurrence again refused to have surgical intervention and was re-treated with imiquimod for 10 weeks (instead of the previous 6 weeks). This subject experienced a better reaction after re-treatment with imiquimod and has had no signs of recurrence after an additional 10 months of follow-up. The subject with the BCC recurrence also experienced a better outcome after the second imiquimod treatment regimen because affected areas were cleared of residual tumor at follow-up. Because of the size and types of tumors, we were expecting more residual tumors to be found with repeat biopsies and higher recurrence rates. Therefore, both subject groups experienced improved cure rates with adjunctive imiquimod therapy compared with historical rates for ED&C alone. Although cosmetic concerns did not affect our decision about treatment, excellent cosmetic results were achieved despite areas undergoing repeat biopsies.

Conclusion

In our clinical experience, topical imiquimod as adjunctive therapy to ED&C was safe and well-tolerated, with minimal unfavorable cosmetic effects. The noninvasive characteristics of imiquimod and the lack of scarring make it especially appropriate for elderly patients and patients who cannot tolerate or do not want extensive surgical therapy. We do not recommend that patients with high-risk BCC or SCC be treated with ED&C and adjuvant topical imiquimod if traditional surgical options are available and if the patient is able to tolerate the procedures. Long-term cure rates are well-established with these methods and should be considered first-line therapy. However, in this limited short-term study, adjuvant topical imiquimod cream was effective in treating both BCCs and SCCs, with only 4 recurrences reported at a median follow-up of 26 months. It appears that the better the response to imiquimod, the more likely the tumor will not recur. The subjects who had recurrences in this study had only mild to moderate reactions to imiquimod treatment. Additional studies are certainly warranted to investigate adjuvant topical imiquimod therapy after ED&C because of the improved cosmetic results and, possibly, improved cure rates with this combination regimen.

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