Long-Term Follow-Up Results of Topical Imiquimod Treatment in Basal Cell Carcinoma

Seher Bostanci, MD,* Pelin Kocyigit, MD,* Seçil Vural, MD,* Aylin Okcu Heper, MD,† and Ayşenur Botsali, MD*

BACKGROUND Imiquimod 5% topical cream is approved for treatment of superficial basal cell carcinoma (BCC). Data on the long-term efficacy and usage in other BCC subtypes are scarce.

OBJECTIVE Evaluation of long-term safety and efficacy of topical imiquimod treatment in various BCC subtypes and locations, with individualized treatment duration.

MATERIALS AND METHODS Histopathologically confirmed BCCs treated solely with topical imiquimod were identified retrospectively and included in this study. Clinical and histopathologic tumor clearances were the primary end point. After treatment was concluded, patients were examined every 3 to 6 months.

RESULTS In total, 24 BCC samples from 22 patients (F:M = 9:13; mean age: 73.5 years, SD: 10.767) were evaluated. The majority of the lesions were located in the head and neck area (83%). Mean treatment duration until complete clearance was 15.7 ± 6.9 weeks (6–28 weeks). Imiquimod was discontinued in 3 lesions, due to either clinically or histopathologically insufficient response. During follow-up, 2 lesions recurred, at 42 and 50 months after treatment. During a mean follow-up time of 72.7 (SD = 9) months, 79.1% of the lesions were cured without local recurrence.

CONCLUSION Although imiquimod is only approved for superficial BCC, treatment success was high among the study patients with various histological subtypes, with good long-term cosmetic results.

The authors have indicated no significant interest with commercial supporters.

Basal cell carcinoma (BCC) is the most frequent malignant tumor among human populations worldwide, and its incidence has been increasing over the last decade. Basal cell carcinoma tends to grow slowly, it rarely metastasizes, and it has a very low mortality rate. However, there are several histologic subtypes of BCC that show significantly more destructive features, with different histological behavior and clinical outcomes.

The gold standard treatment for BCC is surgery. However, surgery can lead to unwanted cosmetic results, especially in the case of large lesions. Additionally, surgical intervention may be difficult in specific localizations and in aged patients with comorbidities. Another factor that may necessitate an alternative treatment approach is patient preference for a nonsurgical approach. In such circumstances, topical immunotherapy with imiquimod 5% cream is an emerging therapeutic option.

Imiquimod 5% cream (brand name: Aldara or Zyclara) is an immunomodulatory drug that acts by activating Toll-like receptor 7, which stimulates the epidermal and dermal dendritic cells to produce cytokines and attract natural killer cells while enhancing proliferation of B lymphocytes.[1] It has been approved by the United States Food and Drug Administration for the treatment of actinic keratosis, external genital warts, and superficial BCC.[2–4] In recent years, imiquimod has been reported to be effective in off-label use as a treatment for giant BCC, infiltrative BCC, and BCCs located in high-risk

*Departments of *Dermatology, and †Pathology, Faculty of Medicine, Ankara University, Ankara, Turkey; S. Vural is currently affiliated with the Dermatology and Allergology Department, Ludwig Maximilian University, München, Germany*

ISSN: 1076-0512 • Dermatol Surg 2018;44:36–41 • DOI: 10.1097/DSS.0000000000001266

areas, in a limited number of patients.[5,6] In the recent Surgical excision versus Imiquimod 5% cream for Nodular and Superficial basal-cell carcinoma (SINS) trial, even though it was inferior to surgery, imiquimod was shown to be an effective treatment for superficial and small nodular BCCs.[7]

In this retrospective study, the authors investigated the efficacy of imiquimod in the treatment of different BCC subtypes, and the rate of recurrence in long-term follow-up.

Methods

The study was carried out in the Dermatology Department in Ankara University. Study inclusion criteria were as follows: a pathologically confirmed BCC diagnosis, refusal of surgical intervention, and treatment with imiquimod 5% cream as sole treatment. Patients treated only with imiquimod were extracted from the database, retrospectively. All patients had given their informed consent. Clinical characteristics, including age, gender, localization of tumor, initial pathological subtype of BCC, initial size of the tumor, clinical clearance, post-treatment pathology results, follow-up duration, and side effects, were recorded. Criteria for treatment efficacy were clinical and histopathologic tumor clearance and absence of recurrence during the follow-up period. Histopathologic clearance was evaluated by an incisional biopsy performed at the third month follow-up visit after the end of therapy. Every patient included in the study had received a standardized protocol for imiquimod therapy. Treatment was initiated in all patients as topical application of imiquimod 5% cream on 5 consecutive days per week for 6 weeks. Patients were instructed to apply the cream uniformly as a thin layer over the lesion and leaving the cream on the lesion for about 8 to 12 hours before washing it off. To target possible subclinical tumor extension, the treatment area was extended to cover a 1-cm radius beyond the visible margins of the lesion. In the case of severe irritation, treatment was paused for 1 to 4 days, depending on degree of irritation, and then resumed. Irritation was a common side effect throughout the treatment period; however, irritation severe enough to warrant discontinuation of treatment was not observed. Lesions were clinically reevaluated at the end of 6 weeks. In the case of no or insufficient response, treatment was discontinued. Insufficient clinical response was defined as less than 25% decrease in tumor size. In responders, treatment duration was extended, with examinations every 2 weeks, until complete clinical response was achieved. Treatment was discontinued after total clearance of the tumor. Patients were examined every 3 months for the first 2 years after treatment cessation and every 6 months thereafter. Patients were also informed about signs of recurrence and advised to come in earlier if they observed any change in the location of the former tumor.

Statistical analysis was done with SPSS Statistics 21.0 (IBM).

Results

A total of 24 BCC lesions from 22 patients (13 men, 9 women; mean age [±SD]: 73.5 [±10.767] years) were evaluated. Lesions were located predominantly on the head and neck region (n = 20 [83.3%]). Lesional characteristics and treatment outcomes are summarized in Table 1. The distribution of the lesions was as follows: 14 nose, 1 forehead, 1 suborbital area, 3 ears, 1 sulcus nasolabialis, and 4 on the trunk. Histopathologically, all tumors fulfilled the standard criteria for the diagnosis of BCC. Basal cell carcinoma subtypes of all lesions were determined by skin biopsy before treatment and were nodular (12), micronodular (2), superficial (3), metatypical (2), and infiltrative (5). Of the 24 BCC lesions, 22 were primary and 2 were recurrent (1 superficial and 1 infiltrative subtype). Both the recurrent tumors were located on the nose and had recurred after total excision and skin grafting. Mean treatment duration until complete tumor clearance was 15.7 ± 6.9 weeks (6–28 weeks). Post-treatment biopsy was performed in 18 of these lesions, whereas in 6 lesions, post-treatment biopsy was not performed because patients refused the procedure.

Complete clinical response was observed in 22 of the lesions (91.7%) by the end of treatment. Pretreatment and post-treatment photographs are shown in Figure 1. In the 2 lesions evaluated as "insufficient clinical response," treatment was discontinued due to only

a partial decrease in diameter of the tumor. The initial subtypes of the 2 clinically nonresponsive lesions were infiltrative and nodular. Post-treatment diagnostic confirmation biopsies from these lesions were consistent with metatypical and nodular BCC, respectively. In 1 of the 22 clinically responsive lesions, post-treatment confirmation biopsy was consistent with metatypical BCC, despite its full clinical response. The initial histological subtype of this lesion was solid BCC. Overall, the rate of both histological and clinical treatment response was 87.5% (21/24 cases) by the end of the treatment period. The mean follow-up duration was 72.7 months (range, 42–86 months). During follow-up, 2 lesions recurred, one in the 42nd month and the other in the 50th month. The recurrence rate was 9.5% (2/21). Both of these lesions were diagnosed as metatypical BCC in the pretreatment histopathology analysis. Long-term treatment success was calculated as 79.1% (19/24 tumors) at 6-year follow-up, in this study.

During the treatment period, local skin reactions, such as erythema, scaling, dryness, crusting, ulceration, and burning sensation, were present in the majority of patients (81%). However, these skin reactions were mild to moderate in all patients and none of the patients quit treatment. Hypopigmentation/depigmentation was present in 71% (17/24) of the lesions immediately after treatment and 6 months later. Hypopigmentation/depigmentation eventually healed, with normal skin pigmentation, in all patients.

TABLE 1. Summary of Patient Characteristics and Treatment Outcome

Case	*Age, yrs*	*Sex*	*Localization*	*Initial HP*	*Treatment Duration, wks*	*CC*	*RB*	*HC*	*Follow-Up Duration, mo*	*Relapse*	*Diameter, mm*
1	75	F	Nose	Infiltrative	16	–	+	–*	—	UR	13 × 12
2	62	M	Suborbital	Nodular	12	+	+	+	74	–	10 × 10
3	80	M	Nose	Infiltrative	11	+	+	+	68	–	13 × 8
4	55	M	Trunk	Superficial	27	+	+	+	80	–	40 × 30
5	70	M	Nose	Metatypical	14	+	+	+	50	+	10 × 7
6	62	F	Nose	Superficial	24	+	+	+	74	–	14 × 12
7	78	M	Ear	Nodular	20	+	–	NA	86	–	10 × 10
8	53	F	Nose	Micronodular	16	+	+	+	80	–	15 × 10
9	82	M	Frontal	Infiltrative	20	+	–	NA	62	–	15 × 12
10	70	F	Nose	Superficial	7	+	–	NA	62	–	12 × 9
11	73	F	Nose	Nodular	10	+	+	+	62	–	12 × 10
12	62	F	Nose	Nodular	28	–	+	–	—	UR	13 × 11
13	79	M	Ear	Nodular	10	+	+	+	62	–	12 × 10
14	53	M	Nose	Infiltrative	22	+	+	+	77	–	15 × 14
15	80	F	Nose	Nodular	12	+	–	NA	70	–	12 × 12
16	85	M	Trunk	Nodular	10	+	+	+	62	–	18 × 15
17	85	M	Trunk	Nodular	6	+	+	+	62	–	16 × 9
18	85	M	Trunk	Nodular	6	+	+	+	62	–	15 × 10
19	76	M	Nose	Nodular	16	+	+	–*	—	UR	12 × 9
20	70	F	Ear	Nodular	28	+	–	NA	86	–	14 × 10
21	81	M	Nose	Infiltrative	16	+	+	+	80	–	12 × 10
22	96	M	Nose	Micronodular	16	+	+	+	86	–	15 × 13
23	74	F	Nasolabial sulcus	Metatypical	8	+	+	+	42	+	11 × 9
24	68	M	Nose	Nodular	24	+	–	NA	86	–	12 × 8

*Metatypical histopathology.

CC, clinical clearance; HC, histological clearance; HP, histopathology; NA, not available; RB, re-biopsy; UR, unresponsive.

Discussion

Excisional surgery is the gold standard in treatment of BCC. However, in the case of elderly patients, patients who are reluctant to undergo surgery, or patients with lesion locations where surgery may lead to unwanted cosmetic results, alternative treatment modalities are needed. Although topical application of imiquimod 5% cream is effective in small (<7.5 mm), superficial BCCs, its success rate in high-risk locations, and for BCC subtypes other than superficial BCC, is not well documented. In this study, the authors included tumors greater than 1 cm diameter with various subtypes of BCC including aggressive variants (infiltrative, metatypical, and solid). Treatment response was 87.5% at the end of the treatment period (21/24 cases). A mean of 72.7 months of follow-up duration after treatment gave us a source of reliable retrospective data on success rate. Long-term treatment success was calculated as 79.1% (19/24 tumors) at 6-year follow-up, in this study. This rate is compatible with the 5-year treatment success after 6 weeks of application of imiquimod, 5 days per week, to superficial BCCs observed in the study by Gollnick and colleagues[8] (77.9%). The treatment success of imiquimod for superficial BCC has been reported in the literature as between 69% and 100% by the end of the treatment period, with a 5 d/wk regimen.[8,9]

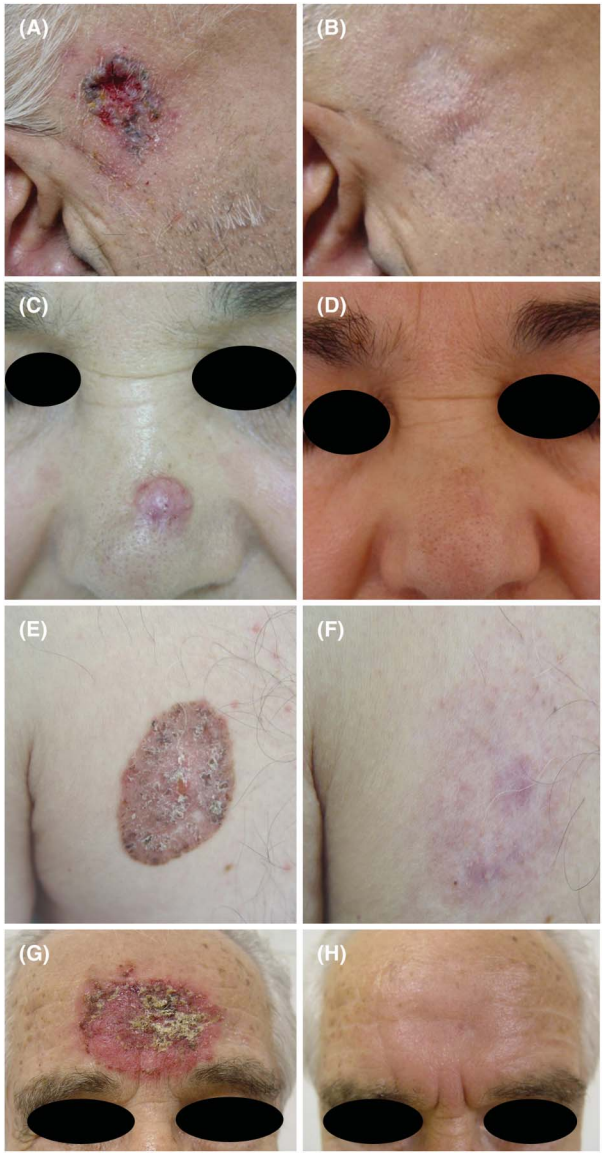

Figure 1. (A) Pretreatment and (B) post-treatment photographs of an infiltrative BCC on temporal area; (C) pretreatment and (D) post-treatment photographs of a nodular BCC with 16 weeks of imiquimod treatment; (E) pretreatment and (F) post-treatment photographs of a superficial BCC with 27 weeks of imiquimod treatment; (G) pretreatment and (H) post-treatment photographs of an infiltrative BCC with 20 weeks of topical imiquimod therapy. BCC, basal cell carcinoma.

Sterry and colleagues compared the efficacy of 2- or 3-day imiquimod application with or without occlusion in superficial and small low-risk nodular BCCs. In the nodular BCC group receiving the 3 d/wk regimen, the histological clearance rate was 50% without occlusion and 65% with occlusion, respectively. There was no statistically significant difference between 4 treatment regimens among patients with nodular BCC at the end of the treatment period.[5] The occlusion of the lesion site after imiquimod application is not recommended because this approach does not seem to confer additional benefits.

In the SINS trial, investigators had compared imiquimod to surgical excision in superficial and nodular BCCs in a large group of patients. Treatment protocol for nodular BCCs was daily application of imiquimod 5% cream without occlusion for 12 weeks. Even though imiquimod was less effective than surgery among nodular BCCs (81.8% vs 98.9% at 3-year follow-up), the treatment success was satisfactory. Cosmetic appearance after 3 years was significantly superior in the imiquimod group (60.6% vs 35.6%).[7]

The efficacy of imiquimod treatment for nodular BCCs located in high-risk areas was previously demonstrated in a study of 19 periocular BCCs. At the 3-year follow-up, the histological clearance rate was 81.8% among nodular BCCs with a diameter greater than 1 cm.[6] Imiquimod

was used before Mohs micrographic surgery in 12 nodular BCCs on the nose, with a treatment protocol of 5 applications per week for 8 to 16 weeks. However, only 42% tumor clearance was achieved.[10] The authors speculated about the possibility that nasal BCCs might be resistant to imiquimod treatment, compared with nodular or superficial BCCs of other sites. In accordance with that study, long-term treatment response of nasal BCCs in this study was 63% (7/11), despite prolonged therapy. The success rate of imiquimod treatment for BCCs was much lower than that for tumors located elsewhere (92% [12/13]). Imiquimod treatment of nasal BCCs should therefore be considered cautiously and used only if the patients cannot tolerate other treatment modalities.

The immune system plays an active role in BCC surveillance.[11–13] Hence, immune response in BCC can be modulated by intralesional injections of interferon or by topical application of imiquimod, each resulting in clearance of the tumor. Imiquimod leads to the activation of both innate and acquired immune systems via Toll-like receptor 7.[14] Basal cell carcinoma is caused by aberrant activation of the hedgehog/glioma-associated (GLI) oncogene pathway, mostly due to genetic inactivation of the "patched" gene or activation of "smoothened."[15,16] Recently, it was shown that imiquimod also acts by stimulating adenosine receptor/protein kinase A–mediated GLI phosphorylation, thus directly inhibiting hedgehog signaling.[17]

The authors' findings support imiquimod cream as a strong alternative for different BCC subtypes. After a mean follow-up of 70 months, only 2 relapses were observed among the 21 patients with a complete response. These 2 relapses were 2 BCCs with metatypical pathology at 3.5 and 4 years after treatment. Metatypical BCC is a rare subtype of BCC composed of a complex of tumors characterized by both basaloid and squamoid differentiation, in an apparent continuum between BCC and squamous cell carcinoma (SCC). The prognosis for metatypical carcinoma reflects the histopathology of the tumor and is worse than that for classical BCC. The recurrence rate is also reported to be higher than for classical BCC.

An interesting finding in this study is that post-treatment confirmation biopsies of 2 lesions that were compatible with nodular and infiltrative type BCC before treatment were consistent with metatypical BCC after 6 weeks of treatment with imiquimod. Recently, development of SCC on 3 BCC lesions treated with vismodegib has been reported.[18] Vismodegib is a potential hedgehog pathway inhibitor. Authors concluded that either the initial lesion was a metatypical BCC and only the BCC part benefited from treatment or the hedgehog pathway inhibition may have induced squamous differentiation in some stem cells normally located in the deep epidermal layer or near the follicular bulge. In this study, the 2 lesions with conversion to metatypical BCC may be the result of imiquimod acting in a similar way, by hedgehog pathway inhibition. It is also possible that the initial lesion was a mixed-type BCC and the previous biopsy was from a BCC-dominant location. In most of the previous studies, histological clearance rates were analyzed, but detailed histopathology results were not reported.[9,19,20] In a longitudinal follow-up study of infiltrative BCC patients, only 1 of 37 patients had a relapse and the histological subtype of the lesion was consistent with infiltrative BCC on post-treatment biopsy.[21]

Most commonly reported side effects during treatment with imiquimod are due to the local irritation effect of the agent. Severe side effects including retinal vein occlusion (following treatment of a periorbital BCC), bilateral pulmonary embolism, and permanent vitiligo-like depigmentation were also reported.[22–24] In this study, mild to moderate local skin irritation was commonly observed. Although hypopigmentation/depigmentation did develop on healing lesions, that depigmentation was temporary.

An important strength of this study was that, instead of a standardized 6-week treatment, the treatment duration was individualized to each patient/lesion, according to treatment response. Treatment duration varied between 6 and 28 weeks. The authors recommend prolonging therapy when lesions show incomplete response at the end of 6 weeks. Another important point is that this study included patients with different BCC subtypes and lesions from high-risk locations, such as nose, periorbital area, and ear; imiquimod was effective in the treatment of these high-risk location BCCs. Also, both treatment success and recurrence rates were effectively evaluated via a long follow-up duration.

This study has some limitations. First of all, histological clearance was demonstrated with incisional biopsies in this study. This may have resulted in some cases with false interpretation of total histological clearance since the biopsy may have missed the area with tumor tissue. Second, in some of the lesions, post-treatment histological clearance could not be demonstrated with biopsy because of patients' preference. Those lesions were only clinically evaluated. Another limitation is that while many subtypes of BCCs were included in the study, the study was not designed to evaluate imiquimod's efficacy for any specific BCC subtype.

Conclusion

Surgery remains the best treatment for BCC. However, patient eligibility status (e.g., comorbidities that make surgery a less optimal choice), lesion characteristics, and localization may direct clinicians toward alternative treatment options. Imiquimod topical treatment offers an effective and simple treatment option with optimal cosmetic results. In this study of BCC patients with different histological subtypes, including lesions located in high-risk areas, treatment success was 79.1% over 6 years of follow-up. Among different histological subtypes, imiquimod treatment should be avoided in metatypical carcinoma because of the aggressive biology of the tumor.

References

1. Schon MP, Schon M. Imiquimod: mode of action. Br J Dermatol 2007; 157(Suppl 2):8–13.
2. Kircik L, Sung JC, Stein-Gold L, Goldenberg G. United States Food and drug Administration product label changes. J Clin Aesthet Dermatol 2016;9:39–48.
3. Chun-Guang M, Qi-Man L, Yu-Yun Z, Li-Hua C, et al. Successful treatment of giant basal cell carcinoma with topical imiquimod 5% cream with long term follow-up. Indian J Dermatol 2014;59:575–8.
4. Roldan-Marin R, Toussaint-Caire S. Imiquimod 5% as Adjuvant therapy for incompletely excised infiltrative nodular basal cell carcinoma and dermoscopy to monitor treatment response. Dermatol Ther (Heidelb) 2015;5:265–72.
5. Sterry W, Ruzicka T, Herrera E, Takwale A, et al. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomized studies comparing low-frequency dosing with and without occlusion. Br J Dermatol 2002;147:1227–36.
6. de Macedo EM, Carneiro RC, de Lima PP, Silva BG, et al. Imiquimod cream efficacy in the treatment of periocular nodular basal cell carcinoma: a non-randomized trial. BMC Ophthalmol 2015;15:35.
7. Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15:96–105.
8. Gollnick H, Barona CG, Frank RG, Ruzicka T, et al. Recurrence rate of superficial basal cell carcinoma following treatment with imiquimod 5% cream: conclusion of a 5-year long-term follow-up study in Europe. Eur J Dermatol 2008;18:677–82.
9. Geisse J, Caro I, Lindholm J, Golitz L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol 2004; 50:722–33.
10. Butler DF, Parekh PK, Lenis A. Imiquimod 5% cream as adjunctive therapy for primary, solitary, nodular nasal basal cell carcinomas before Mohs micrographic surgery: a randomized, double blind, vehicle-controlled study. Dermatol Surg 2009;35:24–9.
11. Barnetson RS, Halliday GM. Regression in skin tumours: a common phenomenon. Australas J Dermatol 1997;38(Suppl 1):S63–5.
12. Wong DA, Bishop GA, Lowes MA, Cooke B, et al. Cytokine profiles in spontaneously regressing basal cell carcinomas. Br J Dermatol 2000; 143:91–8.
13. Urosevic M, Dummer R. Immunotherapy for nonmelanoma skin cancer: does it have a future? Cancer 2002;94:477–85.
14. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. J Am Acad Dermatol 2000;43:S6–11.
15. Xie J, Murone M, Luoh SM, Ryan A, et al. Activating Smoothened mutations in sporadic basal-cell carcinoma. Nature 1998;391:90–2.
16. Aszterbaum M, Rothman A, Johnson RL, Fisher M, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. J Invest Dermatol 1998;110:885–8.
17. Wolff F, Loipetzberger A, Gruber W, Esterbauer H, et al. Imiquimod directly inhibits Hedgehog signalling by stimulating adenosine receptor/protein kinase A-mediated GLI phosphorylation. Oncogene 2013;32: 5574–81.
18. Saintes C, Saint-Jean M, Brocard A, Peuvrel L, et al. Development of squamous cell carcinoma into basal cell carcinoma under treatment with Vismodegib. J Eur Acad Dermatol Venereol 2015; 29:1006–9.
19. Shumack S, Rigel D. Treatment of non-melanoma skin cancer: immunotherapy as a viable option. Acta Derm Venereol Suppl (Stockh) 2003:18–22.
20. Beutner KR, Geisse JK, Helman D, Fox TL, et al. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. J Am Acad Dermatol 1999;41:1002–7.
21. Vidal D, Matias-Guiu X, Alomar A. Fifty-five basal cell carcinomas treated with topical imiquimod: outcome at 5-year follow-up. Arch Dermatol 2007;143:266–8.
22. Sriprakash K, Godbolt A. Vitiligo-like depigmentation induced by imiquimod treatment of superficial basal cell carcinoma. Australas J Dermatol 2009;50:211–3.
23. Hong E, Cooper A. Incipient retinal vein occlusion following immunotherapy of periorbital basal cell carcinoma. Australas J Dermatol 2012;53:139–40.
24. Leroy B, Richez A, Wolf F, Descotes J, et al. Imiquimod and pulmonary embolism: a case report. Therapie 2014;69:180–1.

Address correspondence and reprint requests to: Seçil Vural, MD, Department of Dermatology, Faculty of Medicine, Ankara University, Dermatology and Allergology Department, Ludwig Maximilian University, Frauenlobstrasse 9-11 80337 München, Germany, or e-mail: secilsaral@gmail.com