Imiquimod and lentigo maligna: a search for prognostic features in a clinicopathological study with long-term follow-up

A.M. Powell, A.M. Robson, R. Russell-Jones and R.J. Barlow

St John's Institute of Dermatology, Guy's and St Thomas' NHS Trust, London SE1 7EH, U.K.

Correspondence
A.M. Powell.
E-mail: AnnMarie.Powell@gstt.nhs.uk

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Summary

Background Melanoma in situ/lentigo maligna (LM) is a potential precursor of LM melanoma. It occurs most commonly in elderly individuals on sun-exposed skin of the head and neck. Although surgical excision is the treatment of choice, this may not be desirable or feasible for large lesions at functionally or cosmetically important sites. Imiquimod is a topical immunomodulator which can generate a local cytotoxic response with potentially antiviral and antitumour effects.

Objectives To present our experience of LM treated with imiquimod.

Methods A retrospective review was performed of all patients with facial LM treated in our unit with topical imiquimod between January 2001 and December 2006. Pretreatment diagnostic biopsies were also reviewed and histologically graded.

Results Forty-eight patients were treated with imiquimod. There were 37 responders and 11 treatment failures (of whom two were 'partial responders'). Of the 37 responders, 31 showed a clinical inflammatory response to imiquimod. One patient in whom treatment failed subsequently developed invasive disease. The mean follow-up duration was 49 months. We could not identify histological features of prognostic significance. However, the ability to develop an inflammatory reaction to imiquimod was a strong predictor of therapeutic benefit.

Conclusions We consider imiquimod to have a role in the treatment of LM in patients in whom surgery may be contraindicated or for those in whom the cosmetic or functional consequences may be considerable. Until better characterized, its use should probably be confined to centres with experience in the detection and treatment of LM and melanoma.

The features of lentigo maligna (LM) were described by Hutchinson[1] and subsequently by Dubreuilh (lentigo malin des vieillards)[2] over 100 years ago. The aim of treatment is to reduce the risk of invasive disease, the prognosis of which (as in other melanomas) depends on the Breslow thickness and the presence of ulceration. Surgical excision is the treatment of choice, providing a cure in 90% of patients or more as well as a histological specimen for accurate staging. However, complete excision of LM may present difficulties owing to its predilection for the face and because there may be extensive unrecognized subclinical spread.[3] As a result, nonsurgical interventions such as radiotherapy or topical imiquimod are sometimes considered.

Imiquimod belongs to the imidazoquinoline family of small nucleoside-like molecules. These have antiviral and antitumour activity owing to immune modulation and possibly to induction of apoptosis signalling.[4] Imiquimod is licensed in the U.K. for the treatment of anogenital warts, actinic keratoses and superficial basal cell carcinomata. Ahmed and Berth Jones[5] first reported the use of topical imiquimod in the treatment of LM. Since then only three uncontrolled studies have been published,[6–8] the first of these with median follow-up of 12 months[6] and the second, our initial study, with median follow-up of < 12 months.[7] In their review of the subject Rajpar and Marsden[9] highlighted among their concerns the lack of published long-term follow-up data, falling short of the accepted cancer standard of 5 years. We have widened our original cohort of 11 patients to include clinical and histological data on a further 37 patients. We present long-term follow-up data where applicable. We also attempted to identify features on pretreatment biopsies which might allow us to predict the response to treatment.

Table 1 Treatment protocol

1 Diagnostic biopsy (one or more incisional punch biopsies)
2 Apply imiquimod 5% to clinically affected area AND to a 2-cm margin three times per week overnight
3 Review within 4 weeks:
If inflammatory response continue for total 6 weeks
If no inflammatory response increase to daily application for further 6 weeks
4 Review at end of treatment:
If clinical evidence of treatment failure proceed to excision
5 Three months after completion of treatment:
Repeat diagnostic biopsy (one or more incisional punch biopsies)
6 Long-term follow-up (with repeat biopsies if indicated)

Patients and methods

Between January 2001 and December 2006 we treated 48 patients with histologically confirmed facial LM not amenable to simple excision with primary closure. We had excluded patients with histological or clinical evidence of LM melanoma and patients who were immunocompromised. The proposed treatment and alternatives were discussed with all patients and informed consent was obtained.

We used a similar treatment protocol (Table 1) to that of our earlier study.[7] All patients were instructed to apply imiquimod 5% (Aldara®; 3M Healthcare Ltd, Loughborough, U.K.) for 8 h, three times per week, to the clinically affected area and a 2-cm margin of normal surrounding skin. Topical fusidic acid ointment (Fucidin® ointment; Leo Laboratories Ltd, Dublin, Ireland) was applied daily to prevent secondary impetiginization. Patients were reviewed within 4 weeks of starting therapy. If an inflammatory reaction was not elicited by applying imiquimod three times a week, the frequency was increased to daily applications and continued for a further 6 weeks. A repeat 4-mm punch biopsy was performed adjacent to the original diagnostic biopsy scar approximately 3 months after treatment. In patients with residual pigmentation or those with large lesions at presentation, biopsies were taken from at least two sites. Patients who did not respond to imiquimod therapy proceeded to excision (most commonly by the 'slow' Mohs' technique, i.e. with rushed paraffin-embedded sections).

Patient follow-up

Those patients in whom the post-treatment biopsy showed no residual LM were reviewed at 6–12-month intervals. Patients were advised to return sooner if they noticed inflammatory or pigmentary changes at the treated site.

Histopathological review

A search was made for histological features predictive of a response to treatment. Of 48 patients, the diagnostic biopsies of 28 were available for review. In each, the severity of dysplasia was scored according to: (i) degree of lentiginous proliferation; (ii) grade of cytological atypia; (iii) presence of inflammation; (iv) nesting of melanocytes; (v) adnexal spread; (vi) pagetoid spread; (vii) effacement of rete ridges; and (viii) pigmentary incontinence (Table 2 and Fig. 1a,b). For patients with more than one initial diagnostic biopsy the biopsy with the worst (highest) score was used in analysis.

Table 2 Histological criteria and scoring system used to assess degree of histological dysplasia

Histological criterion	Finding	Score
Degree of lentiginous proliferation	Early	0
	Near confluent (i.e. 5–10 melanocytes in a row)	1
	Confluent (i.e. > 10 in a row)	2
Grade of cytological atypia	Mild	1
	Moderate	2
	Severe	3
Presence of inflammation	Perivascular or periadnexal	1
	Moderate to heavy interstitial	2
	Florid	3
Nests of melanocytes	Absent	0
	Present	1
	Florid	2
Adnexal spread	Absent	0
	Present	1
Pagetoid spread	Absent	0
	Present	1
Effacement of rete ridges or epidermal atrophy	Absent	0
	Present	1
Pigmentary incontinence	Absent	0
	Present	1

Results

Patients

Imiquimod immunotherapy was attempted in 48 patients (17 male) with LM. The age range was 44–90 years (mean 70·6). Thirty-two patients had received no previous treatment, with the exception of cryotherapy (n = 5). The remaining 16 patients all had persistent disease following previous attempted excisions of their LM. One of these had also been treated with radiotherapy. The maximum horizontal diameter of clinically apparent disease was 7·5 cm in the largest lesion (mean 2·1 cm). Two patients had wholly amelanotic lesions.

Outcome of treatment

Thirty-seven of the 48 patients (77%) were considered to have responded to imiquimod because they had no clinical or histological evidence of LM at 4–6 months after therapy (or on subsequent long-term follow-up). The remaining 11 patients (23%) were assessed as having failed imiquimod

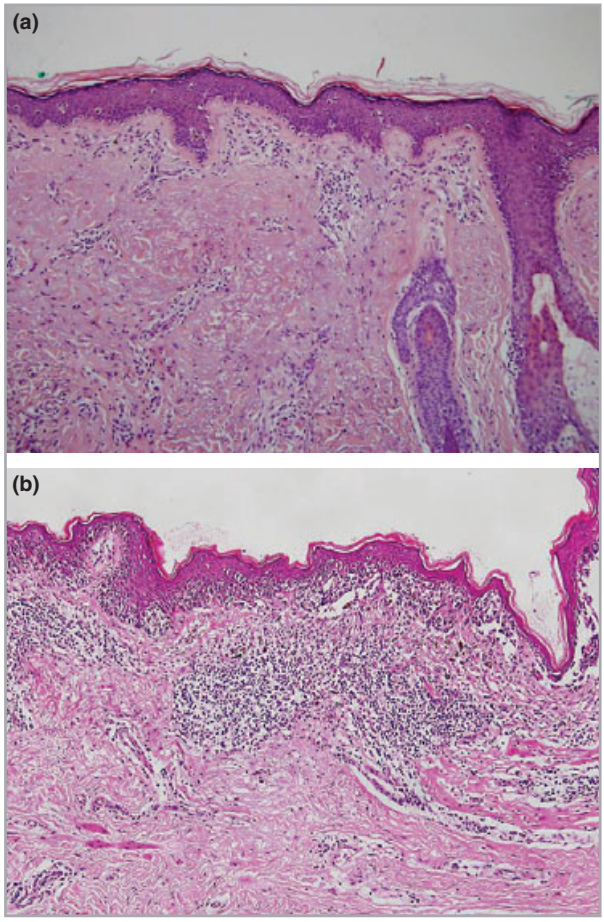

Fig 1. (a) This skin biopsy shows an increased number of atypical melanocytes in a lentiginous pattern at the basal layer with evidence of extension down the adnexal epithelium; the histological 'dysplasia score' of this lesion is 4. (b) This biopsy shows inflamed skin with confluent replacement of the epidermal basal layer and nest formation by atypical melanocytes; the histological 'dysplasia score' of this lesion is 10.

therapy on the grounds that LM was present on the post-treatment biopsy. All of these were submitted for surgical excision of their lesions (seven by 'slow' Mohs' technique). One of the 'nonresponder' group had no evidence of LM on histological examination of the subsequent excision biopsy specimen and may therefore have had a partial response. A second patient appears to have had a significantly smaller residual lesion following application of imquimod and may also have had partial response. In this second patient, the clinical dimensions of the lesion measured 32 × 27 mm before imiquimod treatment whereas the subsequent surgical specimen measured 23 × 19 mm and was reported as having clear margins. A third nonresponder was found to have invasive melanoma (Breslow thickness of 0·46 mm) within the resection specimen, the *in situ* component of which extended to the surgical margin.

The duration of post-treatment follow-up ranged from 25 to 72 months (mean 48·6). Four patients were lost to long-term follow-up (two of whom have died from unrelated causes). There has been no evidence of recurrent disease in the imiquimod-responsive group. Likewise, the imiquimod-nonresponsive group, subsequently treated surgically, has shown no evidence of recurrence.

Inflammatory response to treatment

Six (of 37) responders and nine (of 11) nonresponders failed to show clinical evidence of inflammation during the treatment period.

Three patients were unable to tolerate a complete course of treatment due to marked inflammation and discomfort. At the maximum frequency of application, the inflammatory response was graded as being absent, mild (erythema with pruritus) or brisk (marked erythema with surface change). Only two of the 11 nonresponders developed an inflammatory reaction to imiquimod. These were the patients described above who probably had a partial response. The remaining nine nonresponders had no evidence of irritation or inflammation with imiquimod therapy.

Of the 37 responders, 13 experienced a brisk inflammatory response (complicated by staphylococcal infection in at least three). Eighteen patients developed a mild inflammatory skin reaction. The remaining six patients showed no clinical reaction but still progressed to a satisfactory outcome. A clinically apparent inflammatory response (either mild or brisk) was significantly associated with a therapeutic response (χ^2 16·5, $P < 0{\cdot}00005$; Table 3).

Clinical persistence of pigmentation at completion of therapy was observed in eight of the 37 responders. This represented postinflammatory hyperpigmentation and has faded or disappeared in all cases. No patients have scarred as a consequence of imquimod therapy alone. None of the patients experienced the systemic features of the imiquimod-associated cytokine release syndrome (described as being similar to those associated with systemic interferon therapy).[6]

Prognostic factors

Demographic factors such as the age and sex of the patient did not predict outcome (Table 3). Larger lesions (> 2 cm diameter) were proportionately represented in the responding and nonresponding group (Table 3). Previous treatments (cryotherapy or attempted excision) did not appear to affect outcome (Table 3). Imiquimod application regimen (frequency and duration of treatment) also had no effect on outcome. We blindly reviewed the diagnostic specimens from 28 of the 48 cases (11 nonresponders and 17 responders). This represented an attempt to grade severity and identify histological features that might predict outcome. Subsequent analysis showed no difference between the responding and nonresponding groups in terms of severity. The only features seemingly associated with a positive response were the presence of adnexal spread (χ^2 5·2, $P = 0{\cdot}02$) and demonstration of pigmentary incontinence (χ^2 4·2, $P = 0{\cdot}04$; Table 3).

Table 3 Comparative data for the imiquimod-responsive and nonresponsive groups

Demographic criteria	Responders (n = 37)	Nonresponders (n = 11)
Age (years), mean	72·3	64·2
Male	13/37 (35%)	4/11 (36%)
Failed previous treatment	12/37 (32%)	4/11 (36%)
Maximum diameter of lesion at presentation < 2 cm (n = 31)	24 (78%)	7
Maximum diameter of lesion at presentation > 2 cm (n = 17)	13 (76%)	4
Previous intervention	**Responders**	**Nonresponders**
No prior treatment (n = 23)	17 (74%)	6
Cryotherapy (n = 5)	4 (80%)	1
Excision 1 attempt (n = 8)	6 (75%)	2
Excision > 1 attempt (n = 7)	6 (86%)	1
Excision > 1 attempt AND radiotherapy (n = 1)	1	–
Histological criteria, mean ± SD score	**Responders (n = 17)**	**Nonresponders (n = 11)**
Degree of lentiginous proliferation	1·47 ± 0·8	1·54 ± 0·67
Grade of cytological atypia	2·53 ± 0·62	2·36 ± 0·51
Presence of inflammation	0·65 ± 0·61	0·9 ± 0·79
Nests of melanocytes	1·24 ± 0·83	1·18 ± 0·62
Adnexal spread[a]	1·0 ± 0·00	0·72 ± 0·45
Pagetoid spread	0·24 ± 0·44	0·36 ± 0·39
Effacement of rete ridges or epidermal atrophy	0·35 ± 0·49	0·55 ± 0·51
Pigmentary incontinence[a]	0·94 ± 0·24	0·63 ± 0·49
Total	8·41 ± 4·35	8·55 ± 4·06
Inflammatory response to treatment	31/37 (84%)	2[b]/11 (18%)

[a]These features were seemingly associated with a positive response; [b]these two patients were 'partial responders'.

Discussion

LM usually presents on chronically sun-exposed areas (typically the face) of middle-aged and elderly individuals. It is characterized clinically by a variably pigmented and slowly enlarging patch. The risk of dermal invasion and therefore of progression to LM melanoma is unknown, with estimates varying widely.[10,11] The treatment of choice for LM is surgical excision, current guidelines recommending surgical margins of 0·5 cm of clinically normal skin.[3,12] However, this may be impractical or impossible especially in elderly subjects with large lesions or in those with extensive subclinical spread.

Imiquimod is a topical immune response modifier which acts through toll-like receptor 7 and the NF-κB pathway to enhance both innate and acquired immunity and generate a cytokine milieu favouring a Th1-mediated, cytotoxic response. It is active against both intracellular viral infections and cancers.[13,14]

The advantages and disadvantages of topical imiquimod as a potential treatment for LM have been discussed previously.[7,9] The major disadvantage is the lack of tissue for histological examination of margins. In addition, post-treatment biopsies may be associated with sampling error and may miss residual foci of LM or even LM melanoma. Within the literature and within this series are patients in whom there was either unrecognized invasive disease or progression to LM melanoma during treatment.[6,15] The patient reported by Fisher and Lang[15] is of particular concern because of an apparent clinical response to imiquimod followed by the rapid development of an amelanotic nodular melanoma. A second case report describes recurrence of LM 9 months after treatment.[16] Patients must be counselled about the risk of recurrence and there is a need for on-going patient vigilance as well as long-term patient follow-up.

On the other hand, the advantages of imiquimod include the potential to avoid cosmetically disfiguring surgery particularly in the elderly or debilitated. Furthermore, clinically inapparent extension of disease can be treated by applying imiquimod to surrounding clinically normal skin. This has led Geisse[17] to advocate the delayed use of imiquimod to prevent recurrences after narrow-margin Mohs' surgery for facial LM. Additionally, and as demonstrated by the two 'partial responder' patients in our series, a further advantage may be the potential of imiquimod to 'shrink' the dysplastic area. Imiquimod may have resulted in smaller post-treatment excisions in these patients.

We are still unclear as to the optimal protocol for the use of imiquimod in the treatment of LM. We were unable to identify histological features that identify patients likely to respond to imiquimod. It is difficult to understand our observation of a correlation between adnexal spread and a positive response to imiquimod. One might expect the opposite with a topical treatment.

Our previous experience would suggest deferment of the post-treatment biopsy until at least 3 months after completion of therapy. This can be reconsidered if treatment has failed to elicit an inflammatory response and/or if there is persistence of abnormal pigment. Biopsies performed too soon after treatment are difficult to interpret because of an often florid interface dermatitis. The presence of continuing inflammatory activity suggests that the full effect of treatment is not seen until some time after application of imiquimod is ceased. This may explain why one of the two 'partial responders' had evidence of residual LM within a biopsy taken 2 weeks after completion of therapy but was found to have no LM within the excisional biopsy performed 2 months later. Persistent pigment is often just postinflammatory in nature.

The development of an inflammatory response to imiquimod therapy was significantly associated with, and is likely to be an important element in, the clearance of LM. These data are consistent with the current understanding of the mechanism of action of imquimod, and support our policy of manipulating treatment in order to achieve an inflammatory reaction. Nevertheless, six (of 37) responders had no clinical evidence of any inflammation with treatment. It is possible that any inflammation was subclinical or that there is an alternative mechanism of action of imiquimod. In addition, although an inflammatory reaction seems predictive of treatment responsiveness, patients in our own series as well as a previously reported case raise the possibility of a partial response to imiquimod.[15]

In conclusion, we have presented our experience of LM treated with imiquimod. Many patients were treated more than 5 years ago and show no signs of persistent disease. The response rate within our series (79%) is lower than the 98% reported by Naylor *et al.*[6] after daily treatment for 3 months. Our figure is also lower than the 88% composite response rate calculated by Rajpar and Marsden.[9] We consider imiquimod to have a role in the treatment of LM in patients in whom surgery may be contraindicated or for those in whom the cosmetic or functional consequences may be considerable. The major disadvantage of this treatment is that the entire lesion is not available for histological analysis and incisional biopsies are subject to sampling error. Until better characterized, its use should probably be confined to cancer centres with experience in the detection and treatment of LM and melanoma.

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