Efalizumab-Associated Papular Psoriasis

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Background: Efalizumab is a human anti-CD11a monoclonal antibody used in the treatment of patients with moderate to severe plaque psoriasis. Some of the patients develop new papular lesions during treatment, which are predominantly located in the flexural regions.

Observation: Four patients with recalcitrant psoriasis undergoing treatment with efalizumab presented with erythematous, partly scaly papules and small plaques on previously unaffected areas after 4 to 10 weeks of efalizumab therapy. Tissue sections of biopsy specimens were stained with hematoxylin-eosin, and immunohistochemical staining was performed using monoclonal antibodies against CD3, CD4, CD8, T-cell–restricted intracellular antigen 1, granzyme B, neutrophil elastase, CD68, CD1a, CD11c, HLA-DR, CD25, CD20, and CD56. Histopathological and immunohistochemical examination of the lesions showed features consistent with psoriasis and activation of various leukocyte subtypes including T cells, dendritic cells, macrophages, and neutrophils.

Conclusions: Papular eruptions appearing during efalizumab therapy represent new psoriatic lesions and could be referred to as efalizumab-associated papular psoriasis (EAPP). They usually do not necessitate termination of efalizumab therapy and may optionally be treated with topical corticosteroids. Dermatologists should be aware of these lesions and inform their patients accordingly.

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Psoriasis vulgaris is an immune-mediated inflammatory skin disease that affects 1% to 3% of the world’s population. Cellular changes in the skin include altered keratinocyte differentiation, hyperplasia of the epidermis, and vascular hyperplasia and ectasia together with infiltration of the skin by T lymphocytes, neutrophils, and dendritic cells (DCs). Efalizumab is a recombinant humanized monoclonal antibody that binds to the CD11a subunit of lymphocyte function–associated antigen 1. Efalizumab inhibits the interaction of lymphocyte function–associated antigen 1 with intercellular adhesion molecule 1, thus blocking multiple steps in the immune cascade involved in the development and maintenance of psoriatic plaques, including T-cell activation and trafficking into sites of inflammation.

Clinical studies have demonstrated the efficacy and safety of efalizumab for the treatment of patients with moderate to severe plaque psoriasis. Common adverse events associated with efalizumab include flu-like symptoms (eg, headache, chills, fever, and myalgia) after the first 1 or 2 injections of efalizumab. In addition, the appearance of new potentially psoriatic skin lesions and the worsening of preexisting psoriasis plaques have been also reported during efalizumab therapy and have been referred to as localized mild breakthrough (LMB) (also termed transient localized papular eruption or transient neutrophilic dermatoses), estimated to occur in approximately one-quarter to one-third of patients, and a more infrequent and extensive eruption known as generalized inflammatory flare (GIF) estimated to occur in 1% to 3% of patients. Localized mild breakthrough consists of localized papules and plaques that arise in previously unaffected areas, eg, the flexural regions (axillae and groin), neck, and torso. It usually occurs within 4 to 8 weeks of initiating efalizumab therapy. Although some authors postulated that LMB is a form of psoriasis occurring during efalizumab therapy, the exact nature of the eru-
tion is still unknown. In this study, we describe 4 patients with psoriasis who experienced cutaneous eruptions similar to those described previously as LMB. In addition, we analyzed the histopathological and immunohistochemical findings of skin biopsy specimens obtained from these lesions with the aim of providing a detailed description and an understanding of their nature.

**REPORT OF CASES**

Four patients (1 woman and 3 men, aged 42-59 years) with recalcitrant psoriasis were treated with weekly subcutaneous injections of efalizumab (1 mg/kg of body weight). The clinical data are summarized in Table 1. All patients had long-standing plaque psoriasis, and the female patient had concomitant severe palmoplantar pustular psoriasis. After 3 to 6 weeks of efalizumab therapy, signs of improvement of their original psoriatic plaques were observed. During the 4th to 10th weeks, all 4 patients developed nonitchy, well-demarcated, erythematous, partly scaly papules and some small plaques (1-2 cm in diameter) on previously unaffected areas. During the 4th to 10th weeks, all 4 patients developed nonitchy, well-demarcated, erythematous, partly scaly papules and some small plaques (1-2 cm in diameter) on previously unaffected areas (Figure 1). Pustular lesions were not observed. The new papular lesions were particularly noted in the flexural regions (axillae and groin) and on the trunk and extremities. No additional medications had been administered, and no signs of underlying infection were detected at the time of eruption of these papular lesions. In 3 patients, laboratory test results indicated absolute lymphocytosis. Treatment with efalizumab was continued, and the papular lesions were treated with midpotent topical corticosteroids once daily. In 2 patients, the lesions resolved within 4 weeks. However, 1 patient who irregularly used the topical corticosteroid continued to experience a milder degree of such lesions for as long as 12 weeks. Three patients responded well to efalizumab therapy and achieved at least 75% reduction of the Psoriasis Area and Severity Index score after 12 weeks. However, 1 patient showed an initial amelioration of these papular lesions, but then progressively developed a GIF, which led to termination of efalizumab therapy at week 11.

**METHODS**

After obtaining informed consent from the patients, 5-mm punch biopsy specimens were taken from papular lesions located in the axillae. The biopsied lesions were about 3 days old in 2 patients and 14 days old in the remaining 2 patients. Tissue specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin according to standard procedures. Another biopsy specimen was processed for immunohistochemical analysis. Immunohistochemical studies were performed using the avidin-biotin-peroxidase complex technique as described elsewhere. The primary monoclonal antibodies used for immunohistochemistry are shown in Table 2. In negative control specimens, the primary antibody was replaced with antibody dilution buffer. Furthermore, positive control specimens were stained in parallel with each series.

Immunofluorescence staining for the detection of tumor necrosis factor α (TNF-α) in formalin-fixed, paraffin-embedded sections was performed using anti–TNF-α antibody (R&D Systems, Minneapolis, Minnesota) followed by goat antirabbit antibody (Alexa Fluor 488; Molecular Probes Invitrogen AG, Basel, Switzerland) as described elsewhere. The substitution of the primary antibody with isotype-matched IgG served as negative control. Besides control antibodies, we preincubated anti–TNF-α antibody, 12.5 µg/mL (R&D Systems), with 200 ng of recombinant human TNF-α (R&D Systems) before the staining procedure to further demonstrate specificity.

**HISTOPATHOLOGICAL FINDINGS**

Histological examination of the 5-day-old skin lesions showed mild psoriasiform acanthosis with formation of mounds of parakeratosis, focal hypogranulosis, and mild spongiosis (Figure 1E). The dermis showed capillary dilatation with mild adjacent edema and a perivascular infiltrate consisting mainly of lymphocytes and macrophages in the upper dermis. Exocytosis of lymphocytes overlying the dilated vessels and also in association with...
mild spongiosis was found. Furthermore, focal intracorneal collection of neutrophils (Munro microabscess) was noted. In addition, 1 biopsy specimen showed formation of a spongiform pustule of Kogoj in the subcorneal layer. The histopathological findings of these papular eruptions were consistent with acute psoriatic lesion resembling guttate psoriasis.

Histopathological findings of the 14-day-old lesions also demonstrated typical features of psoriasis and showed a more prominent psoriasiform hyperplasia with areas of agranulosis and overlying parakeratosis (Figure 1G). Focal accumulation of intracorneal neutrophils was typically present. Dermal changes consisted of capillary dilatation and elongation and a predominant perivascular infiltrate of lymphocytes and macrophages in the upper dermis.

IMMUNOHISTOCHEMICAL FINDINGS

A summary of the results and representative staining are shown in Figure 2 and Figure 3. Immunohistochemical analysis of the inflammatory infiltrate of the 5-day-old skin lesions showed a moderate to severe infiltration of CD3+ T cells with focal exocytosis and accumulation of CD3+ T cells in some areas of the epidermis (Figure 2). A slight predominance of CD4+ over CD8+ T cells was found. Immunostaining for neutrophil elastase confirmed the accumulation of intracorneal neutrophils and the marked presence of these cells in the spongiform pustule of Kogoj. Immunoreactivity for the cytotoxic markers T-cell–restricted intracellular antigen 1 and granzyme B was found on some cells in the epidermis and dermis. Immunoreactivity for CD25 was seen on indi-

Figure 1. Clinical appearance of new well-defined erythematous papules and plaques after 4 weeks of efalizumab therapy. Areas over the axilla (A and F) and trunk (B), and a close-up view of the scaly papules (F, inset) (arrow) are shown. Continuation of efalizumab therapy with topical application of corticosteroids resulted in remission of the new lesions (C and D). Histopathological features are consistent with psoriasis (E and G) (hematoxylin-eosin, original magnification ×100).
Individual cells infiltrating the epidermis and dermis, whereas immunoreactivity for CD56+ (natural killer cells) and CD20+ cells (B lymphocytes) was barely detectable (data not shown). Skin lesions demonstrated a moderate to strong expression of HLA-DR+ in the epidermal and dermal infiltrate. We used CD68, CD11c, and CD1a to analyze the presence of macrophage and DC subpopulations. Moderate immunoreactivity for CD68 was present in the dermis, and some CD68+ cells present at the basal layer were found protruding into the epidermis. A large number of CD11c+ cells were found in the dermis. Furthermore, some CD1a+ DCs were observed in the epidermis.

Immunohistochemical analysis of the inflammatory infiltrate of the 14-day-old lesions showed a milder infiltration of CD3+ T cells (CD4+ > CD8+ T cells) (Figure 2), as well as the presence of T-cell–restricted intracellular antigen 1+ and granzyme B+ cells compared with findings in the more acute lesions. Immunostaining for neutrophil elastase was also less prominent and revealed some scattered neutrophils in the dermis and focal collection of these cells within the stratum corneum. Strong immunoreactivity was seen for HLA-DR and moderate to strong immunoreactivity for CD11c and CD68. As in the more acute lesions, only a few CD1a+ cells were observed.

### IMMUNOFLORESCEENCE FINDINGS

Positively stained cells for TNF-α were detected throughout the dermis. There was staining associated with perivascular inflammatory cells and blood vessels in the papillary dermis (Figure 3).

<table>
<thead>
<tr>
<th>Antibody Against</th>
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<th>Source</th>
<th>Antibody Concentration</th>
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**Table 2. Primary Antibodies Used for Immunohistochemical Analysis**

Abbreviation: TIA-1, T-cell–restricted intracellular antigen 1.

*Working concentrations are given where known; dilutions are given for monoclonal antibodies where the immunoglobulin concentration is not specified by the manufacturer.

^{a}Located in Newcastle upon Tyne, England.

^{b}Located in Glostrup, Denmark.

^{c}Located in Uden, the Netherlands.

^{d}Located in Fullerton, California.

In this study, we investigated 4 patients who developed new psoriatic lesions during therapy with efalizumab. The lesions presented clinically as papules and plaques resembling guttate psoriasis. They appeared during the 4th to 10th weeks of treatment, while the preexisting plaques were responding well to efalizumab therapy. The lesions were located in the flexural areas (ie, axillae and/or groin) in all patients and were additionally disseminated on the trunk of 1 patient. On histopathological examination, these lesions showed typical features of acute (resembling guttate psoriasis) or chronic psoriasis. Previous reports have shown that drug-induced psoriasis may demonstrate histopathological features similar to those observed in our cases. Notably, characteristic histopathological signs of psoriasis, such as Munro microabscesses, were found throughout the dermis. Moreover, focal formation of a spongiform pustule of Kogoj was observed in the biopsy specimen of 1 patient. That patient had concomitant palmoplantar pustular psoriasis, possibly indicating the presence of a distinct immunologic background with an increased susceptibility for the recruitment and activation of neutrophils compared with plaque-type psoriasis. Immunohistochemistry results demonstrated that the mononuclear cellular infiltrate consisted mainly of CD3+ T cells, with CD4+ T-cell predominance and CD11c+ and CD68+ cells. Furthermore, production of the proinflammatory cytokine TNF-α was demonstrated by immunofluorescence studies. Taken together, our histological and immunohistochemical data indicate that these papular eruptions represent psoriatic lesions with activation of various leukocytes, including T cells, DCs, macrophages, and neutrophils.

Previous reports indicate that some patients may develop psoriatic adverse events (the onset of new psoriasis morphologies or worsening of psoriasis) during efalizumab therapy. Two main presentations have been described so far, namely LMB, which simulates the papular skin lesions investigated in this study, and a more infrequent and extensive condition known as GEF. Localized mild breakthrough was previously described as...
a transient, papular eruption that typically does not involve the existing psoriatic plaques and is commonly seen on the neck, torso, or flexural areas during the first 4 to 8 weeks of therapy. The exact incidence of LMB is unknown but has been estimated to occur in one-quarter to one-third of the patients receiving efalizumab therapy. It may appear in patients responding or not responding to efalizumab. Furthermore, LMB has minimal impact on the patients' general response to efalizumab and can resolve throughout the treatment period, with or without the use of topical corticosteroids. Most of these features were also present in our patients. However, as demonstrated in 1 of our patients, the lesions may not be exclusively localized but can also be widespread. Moreover,

**Figure 2.** Immunohistochemical findings of skin biopsy specimens obtained from the 5-day-old (A-D and I-L) and 14-day-old (E-H and M-P) papular lesions with activated T lymphocytes and dendritic cells in the epidermis and dermis (original magnification ×100). Neutrophil elastase staining in the 5-day-old lesion (D) shows accumulation of neutrophils within the epidermis (spongiform pustule of Kogoj).
they may take months to resolve, indicating that the current term—LMB and transient localized papular eruption—do not adequately describe these lesions. We believe that an appropriate description of such eruptions could be reached by simply defining their nature. Therefore, we propose the term efalizumab-associated papular psoriasis (EAPP). Carey et al suggested that the occurrence of these lesions does not indicate or predict any further severe psoriasis flare-ups. Although 3 of our patients had a favorable course and achieved a 75% reduction in the Psoriasis Area and Severity Index score, 1 patient developed a GIF, which led to termination of efalizumab therapy. Thus, we recommend close monitoring and treatment of patients with new papular psoriatic lesions, although the risk of developing a GIF might be small.

The underlying pathomechanisms leading to these new psoriatic lesions, particularly in patients responding to efalizumab therapy, remain elusive. Previous reports indicate that a dysfunction of both innate and acquired immune responses are involved in the initiation and maintenance of psoriatic lesions. Nonlesional psoriatic skin is not completely normal but may harbor various cell types such as plasmacytoid DCs and pathogenic effector T cells. In nonlesional skin, these proinflammatory cells seem to be dormant or controlled by down-regulatory mechanisms. The in situ activation of these cells by danger signals such as local trauma or infection may alter the fine balance between proinflammatory and anti-inflammatory signals. The up-regulation of certain pro-inflammatory cytokines, eg, TNF-α and interferon γ, which are not targeted by efalizumab, together with the up-regulation of adhesion molecules (eg, intercellular adhesion molecule 1) and the subsequent recruitment of T cells may then trigger a breakthrough of an acute psoriatic lesion. The fact that flexural areas are highly colonized with microorganisms and more prone to frictional trauma may provide a partial explanation for the appearance of the new psoriatic lesions in these areas. In addition, we speculate that these papular eruptions may occur more readily when lymphocytosis (known to occur in 40% of patients receiving efalizumab) is present. With more pathogenic T cells accumulating in the blood circulation, some may leak into certain areas more prone to danger signals as mentioned already. Indeed, all of our patients had lymphocytosis or high lymphocyte counts. These findings could also partly explain why these lesions are not seen at baseline but tend to occur during the 4 to 10 weeks after induction of efalizumab therapy. Finally, these lesions may represent a minor flare-up that remains limited in severity and resolves with time, because continuing efalizumab administration may prevent further influx of leukocytes (ie, effector T cells) and their local activation in the affected areas.

In conclusion, the papular eruptions appearing during efalizumab therapy in patients responding or not responding to treatment represent new psoriatic lesions and could be named efalizumab-associated papular psoriasis (EAPP). The appearance of these lesions usually does not necessitate termination of efalizumab therapy, and they may optionally be treated with topical corticosteroids with appropriate monitoring of the patient’s condition. Further investigation is warranted to elucidate why such eruptions occur with efalizumab. Dermatologists should be aware of this kind of lesion and inform their patients accordingly.

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REFERENCES