CASE REPORT
Concomitant occurrence of acneiform eruption, alopecia areata, and urticaria during adalimumab treatment in a patient with pustulosis palmoplantaris: Case report and literature review

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ABSTRACT
Adalimumab is a fully human immunoglobulin G1 monoclonal antibody against tumor necrosis factor (TNF)-α that is increasingly used for the treatment of many autoimmune diseases. However, it has also been reported that adalimumab can induce many adverse cutaneous reactions, including paradoxical psoriasiform eruptions. We describe a patient with pustulosis palmoplantaris who developed four cutaneous adverse reactions, including eczematous lesions, acneiform eruption, alopecia areata, and urticaria during adalimumab treatment. A common histopathological finding in these acneiform and urticarial lesions was the presence of eosinophilic infiltrates. Some authors assume that cross-regulation between TNF-α and interferon-α may contribute to development of a clinical spectrum of cutaneous reactions in predisposed individuals undergoing anti-TNF therapy. The use of different biologics, including adalimumab, etanercept, and ustekinumab, did not seem to improve pustulosis palmoplantaris disease activity in our patient.

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Introduction
Adalimumab is a fully human monoclonal antibody against tumor necrosis factor (TNF)-α that is increasingly used for the treatment of many autoimmune diseases, including psoriasis and pustulosis palmoplantaris (PPP), owing to its efficacy and safety. However, it has also been reported that adalimumab induces various adverse cutaneous reactions. We describe a patient with PPP who developed four unusual adverse cutaneous reactions during adalimumab treatment.

Case report
A 50-year-old Taiwanese male who was a smoker presented with recurrent painful pustules with hyperkeratosis and desquamation over his palms and soles since 2008 (Figure 1A,B). PPP was diagnosed. He had been treated with different conventional therapeutic agents, including methotrexate, acitretin, cyclosporine, and topical corticosteroids, with limited effects. He had also experienced mild elevation of liver enzymes due to methotrexate and complained of headaches and hypertension due to high-dose cyclosporine. He was unable to undergo regular phototherapy because he lived in a rural area. He was referred to our hospital in 2009. After screening for tuberculosis and hepatitis B, he received subcutaneous injections of adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL, USA) at a dose of 40 mg every other week in combination with methotrexate (15 mg/week).

However, within 1 week after the third injection of adalimumab, many mildly tender follicular erythematous papulonodules with pustules developed over his face and trunk, especially over the axillae, groin, and buttocks (Figure 2B). Histopathological examination of a skin biopsy from the left cheek revealed a follicular pustule containing keratins with dense neutrophilic and eosinophilic infiltrates. The eosinophils were located mainly in the peri-follicular dermis, whereas the neutrophils and a few eosinophils were located at the orifice of the follicle. No bacterial clumps were found (Figure 2C,D). A pus culture yielded small amounts of coagulase-negative staphylococci and Propionibacterium acnes, and inflamed acne was diagnosed. The peripheral eosinophil count was within normal limits.

One week after the development of acneiform eruptions, a generalized eczematous rash and itchy wheal-like papules and...
plaques developed over the patient’s trunk and extremities. Individual urticarial lesions subsided within 24 hours, whereas the eczematous lesions persisted beyond 24 hours (Figure 3). Moreover, several well-defined hairless patches of up to coin size appeared over his parietal scalp at the same time. No overlying scalp skin changes were found and a hair pull test was positive with exclamation mark hairs (Figure 4). Alopecia areata (AA) was diagnosed clinically. The patient reported that he had not had previous episodes of acne vulgaris, urticaria or AA. A skin biopsy from one of the urticarial plaques over his shoulder showed perivascular and interstitial infiltrates composed of eosinophils, lymphocytes, and neutrophils without vasculitis. Interstitial dermal edema was also noted. The histopathological findings favored a hypersensitivity reaction. When the fourth and fifth doses of adalimumab were given, all of the skin lesions became more severe. Therefore, we discontinued adalimumab and prescribed doxycycline 100 mg twice daily for the acneiform eruptions. Intra-lesional triamcinolone acetonide was also given for the larger inflamed nodules, with good efficacy. However, the urticarial eruptions responded poorly to different oral antihistamines, including levocetirizine, fexofenadine, and desloratadine. He was thus treated with methotrexate (15 mg/week) and cyclosporine (75 mg/day) because both

![Figure 1](A,B) Many pustules with hyperkeratosis and desquamation on the patient’s palms and soles.

![Figure 2](A,B) Many follicular-corresponding erythematous papules, pustules, and nodules were noted over the patient’s face, axillae, groin, and buttocks. (C) Pathology revealed a follicular pustule containing keratins, and neutrophilic and eosinophilic infiltrates. Many neutrophils and a few eosinophils were located at the orifice of the follicle (H&E, 40×). (D) Most eosinophils were located in the perifollicular dermis (H&E, 200×).
drugs have been used for the treatment of PPP and refractory urticaria.

The treatment was then changed to etanercept, a dimeric TNF-α receptor fusion protein, and acitretin (20 mg/day). All of the four cutaneous adverse reactions, including the eczematous lesions, acneiform eruptions, AA, and urticaria, improved gradually, with clinical remission 1, 3, 4, and 7 months after their onset, respectively (Figure 5). However, PPP disease activity persisted despite a 5-month course of etanercept. He was then treated with ustekinumab, a human anti-interleukin-12 and anti-interleukin-23 monoclonal antibody, at a dose of 45 mg by subcutaneous injection (in weeks 0 and 4) in combination with methotrexate (15 mg/week), acitretin (20 mg/day), and low-dose cyclosporine (75 mg/day). Unfortunately, he still experienced frequent recurrence of pustular eruptions on his palms and soles during the 2 months after the second injection of ustekinumab. He was thus kept on cyclosporine and acitretin. The PPP skin lesions improved gradually, with only occasional minor recurrence of pustules on the soles 2 months after he started taking acitretin alone. He also quit smoking during this period. We assume that he is currently in remission from PPP.

Figure 3 (A,B) Generalized wheal-like papules and plaques with many eczematous patches over the patient’s trunk and extremities. (C,D) Close-up images of the urticarial and eczematous lesions.

Figure 4 Several well-defined hairless patches of up to coin size were noted over the patient’s frontal and parietal scalp. No overlying scalp skin changes were found.
Although the exact mechanism for AA development during anti-TNF-α therapy is unknown, it has been suggested that TNF-α blockage could contribute to dysregulation of immune responses leading to the development of AA. 3,25 According to published reports, only four patients have developed urticarial lesions after adalimumab therapy. 18–21 In two cases, the urticaria was accompanied by angioedema. 18,20 However, no pathology was available for these patients.

In addition to AA and urticaria, acneiform eruptions following anti-TNF-α therapy are also rare. To the best of our knowledge, only seven cases (five treated with infliximab and two with adalimumab) have been described in the English literature. Sun et al reported on three patients with acneiform eruptions following anti-TNF-α treatment, two of whom were receiving adalimumab therapy. 24 Most patients developed asymptomatic erythematous follicular papules, pustules or nodules over the face and trunk 1–2 months after therapy initiation. Of the seven documented cases, only two patients had underlying psoriasis. One case with plaque-type psoriasis received infliximab and another case with pustular psoriasis received adalimumab. The severity of acneiform eruptions varied. Some patients improved with doxycycline monotherapy, whereas others needed isotretinoin to control the skin lesions. No detailed histopathological descriptions of acneiform eruptions have been documented previously. In our case, pathology revealed a follicular pustule containing keratins with dense neutrophilic and eosinophilic infiltrates.

The follicular eruptions in our patient showed eosinophilic infiltration and thus drug-induced eosinophilic pustular folliculitis was a possible differential diagnosis. 26 However, eosinophils in eosinophilic pustular folliculitis are predominantly within hair follicles, whereas the eosinophils in our case were located mainly interstitially, with only a few eosinophils at the orifice of the follicle. We did not observe any eosinophilic infiltration into the follicular epithelium or sebaceous glands. Moreover, the clinical morphology was papulonodular lesions, and not papular lesions alone. We added indomethacin to the treatment for 2 months without efficacy. Thus, acneiform eruption seems to be a better diagnosis to cover the possibility of eosinophilic pustular folliculitis. The significance of Propionibacterium acnes in the acneiform eruptions in our patient is unclear, and might represent an infection, colonization, or only contamination. We also assumed that the acneiform eruption was an unusual hypersensitivity reaction, and not true acne vulgaris.

Table 1 Literature review of clinical characteristics and outcomes for patients who developed alopecia areata, urticaria, and acneiform eruptions after adalimumab therapy.

<table>
<thead>
<tr>
<th>Skin reaction</th>
<th>Case No</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Onset after adalimumab</th>
<th>Clinical feature</th>
<th>Treatment</th>
<th>Prognosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia areata (AA)</td>
<td>1</td>
<td>F 23</td>
<td>Rheumatoid arthritis</td>
<td>2 months</td>
<td>Patchy-type AA</td>
<td>Topical dexamethasone</td>
<td>Evolution to AA universalis</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M 34</td>
<td>Psoriatic arthritis</td>
<td>6 months</td>
<td>Patchy-type AA</td>
<td>Potent topical corticosteroids</td>
<td>Evolution to AA universalis</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>F 38</td>
<td>Rheumatoid arthritis</td>
<td>24 months</td>
<td>AA totalis</td>
<td>NA</td>
<td>Evolution to AA universalis</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>F 30</td>
<td>Rheumatoid arthritis</td>
<td>9 months</td>
<td>Patchy-type AA</td>
<td>Topical &amp; systemic corticosteroids</td>
<td>Minimal hair regrowth</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>F 52</td>
<td>Psoriatic arthritis</td>
<td>15 days</td>
<td>Patchy-type AA</td>
<td>IV hydrocortisone &amp; antihistamines</td>
<td>NA</td>
<td>Disappeared 2 hours later</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>F 60</td>
<td>Rheumatoid arthritis</td>
<td>3 months</td>
<td>Urticaria, angioedema and hypotension</td>
<td>No treatment</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2</td>
<td>F 41</td>
<td>Psoriasis</td>
<td>1 week</td>
<td>Urticaria</td>
<td></td>
<td>Less severe with each injection</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>F 31</td>
<td>Behcet’s disease</td>
<td>1 month</td>
<td>Urticaria and angioedema</td>
<td>IV corticosteroids &amp; antihistamines</td>
<td>Disappeared within 24 hours and 36 hours, respectively</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>M 32</td>
<td>Ankylosing spondylitis</td>
<td>1 month</td>
<td>Urticaria</td>
<td>Oral antihistamines &amp; corticosteroids</td>
<td>Disappeared within a few days</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Acneiform eruption</td>
<td>1</td>
<td>M 55</td>
<td>Pustular psoriasis</td>
<td>2 months</td>
<td>Acneiform eruption</td>
<td>Acitretin 25 mg daily</td>
<td>Minimal improvement 1 month later</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M 62</td>
<td>Rheumatoid arthritis</td>
<td>3 months</td>
<td>Acneiform eruption</td>
<td>No treatment</td>
<td>NA</td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

F – female; M – male; AA – Alopecia areata; NA – not available; IV – intravenous.
Interestingly, a common denominator in the histopathological findings for our patient is the presence of eosinophilic infiltrates in the acniform and urticarial lesions. Although we did not perform a biopsy of the AA lesions, eosinophilic infiltration is a common pathologic feature of AA.23 Although the combination of adverse cutaneous reactions observed here has not been previously reported, a common mechanism may be involved in the cause of all the adverse reactions to adalimumab in our case.

Laga et al evaluated the histopathologic spectrum of pсорiasiform skin eruptions associated with TNF-α inhibitor therapy, and found that scattered to numerous eosinophils were observed in most cases (14 out of 16 specimens).24 However, anti-TNF-α drugs seem to elicit a spectrum of cutaneous reactions that go beyond the classical eosinophilic-rich hypersensitivity reaction. The true mechanism between eosinophilic infiltration and TNF-α blocking remains to be fully determined. De Gennes and colleagues proposed that there is cross-regulation between TNF-α and interferon (IFN)-α, which may lead to an increase in IFN-α.25 They also suggested that aberrant IFN-α expression in predisposed individuals during anti-TNF-α therapy may contribute to psoriasiform skin eruptions and lupus-like syndrome. Similarly, acne, AA, and urticaria have been observed in patients receiving IFN therapy.26–28 We propose that overexpression of IFN during anti-TNF-α therapy plays a role in the pathogenesis of the diverse clinical spectrum of cutaneous reactions in predisposed individuals and may partly account for eosinophilic infiltration.

Some authors consider these adverse reactions a class effect of anti-TNF-α agents.3 However, in our patient, the skin lesions improved after changing to etanercept therapy. The different immunosuppressive strength of these two biologics may account for the difference. Moreover, differences in the mechanism of reaction at injection sites have been reported for adalimumab and etanercept.34 We suggest that some adverse cutaneous reactions, such as psoriasiform eruptions, are a class effect, whereas others, such as injection-site reactions, may be drug-specific.

PPP is a challenging disease for which no therapeutic standard has yet been defined; acitretin is the drug of choice according to most recommendations. The difference between PPP and psoriasis has long been debated, and some current therapeutic guidelines do not recommend the use of biologics in PPP because of inconsistent therapeutic responses and a possibly higher risks of adverse cutaneous reactions.35–38 However, most of the drugs used for psoriasis have been used for PPP. Some authors have also suggested that concomitant use of biologic agents and methotrexate has a synergic effect on psoriasis. We thus used acitretin, ustekinumab, methotrexate, and low-dose cyclosporine concomitantly for the patient because of the poor response to previous biologics and the refractory nature of his urticaria and PPP.

Ustekinumab is a new biologic that has been approved for the treatment of moderate to severe plaque psoriasis in many countries. It is a fully human immunoglobulin G kappa monoclonal antibody that binds to interleukin-12 and interleukin-23 and subsequently reduces the activity of T-helper 17 cells. In a recent case series available online, only one out of four patients with PPP experienced good but slow efficacy for ustekinumab, unlike the fast onset of treatment response observed in plaque psoriasis.39 This result is consistent with our experience.

In conclusion, this is a rare case of a patient who showed four adverse cutaneous reactions concurrently following adalimumab treatment for PPP. The pathological findings in our case suggest a shared pathogenic mechanism, but further studies are necessary to clarify the exact causes of adalimumab-related cutaneous side effects. As the use of TNF-α antagonists continues to increase, recognition and management of such side effects will become increasingly important.

References