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Case report

Apremilast in combination with botulinum toxin-A injection for recalcitrant Hailey-Hailey disease

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Hailey–Hailey disease (HHD) is a rare genodermatosis caused by a mutation in the ATP2C1 gene, which codes for a calcium channel. This ionic alteration leads to a defective keratinocyte adhesion. Hailey–Hailey disease is characterized by recurrent flare-ups of vesicles and flaccid blisters in folds that have an impact on patients' quality of life. The recurrent and refractory nature of this condition makes its treatment a challenge. Isolated cases have been reported describing controversial results after treatment with apremilast. Here we present a case of refractory HHD who experienced an excellent response after treatment with apremilast and botulinum toxin-A (BoNT) infiltrations.

A 54-year-old woman with no relevant medical history, except for being slightly overweight, presented with a 30-year history of HHD with a chronic-relapsing course. She reported having followed multiple treatments previously without success. These included topical steroids and calcineurin inhibitors, topical and systemic antibiotics, dapsone, vitamin E, doxepin, oral glycopyrrolate, acitretin, naltrexone, and photodynamic therapy. Physical examination showed erythematous-scaly plaques, with superficial and painful erosions on both latero-cervical regions, armpits, and antecubital fossa of the left arm. Off-label use of apremilast 30 mg twice a day was approved by our hospital's Institutional Review Board. Treatment was well tolerated with mild self-limited diarrhea as the only side effect. The patient experienced a marked improvement with the absence of new flares for 6 months (Fig. 1). However, new erythematous-scaly plaques appeared on both axillary regions during the summer. Apremilast treatment was maintained, and BoNT infiltrations in the armpits were added to control hyper sweating as an aggravating local factor. After one single BoNT infiltration, a great improvement was observed (Fig. 2). After one year of maintained treatment with apremilast, no new flare-ups were observed.

Apremilast is an orally administered phosphodiesterase 4 (PDE4) inhibitor approved for the treatment of psoriatic arthritis that has been successfully used off-label in other conditions. PDE4 is an enzyme widely expressed in macrophages and lymphocytes, as well as non-hematopoietic cells such as keratinocytes. Inhibition of PDE4 has been shown to decrease the production of multiple pro-inflammatory cytokines, such as TNF-α or IFN-γ, while it enhances the anti-inflammatory effect of the cytokine IL-10.[1–3] Apremilast has also been shown to reduce reactive oxygen species (ROS) levels in murine models

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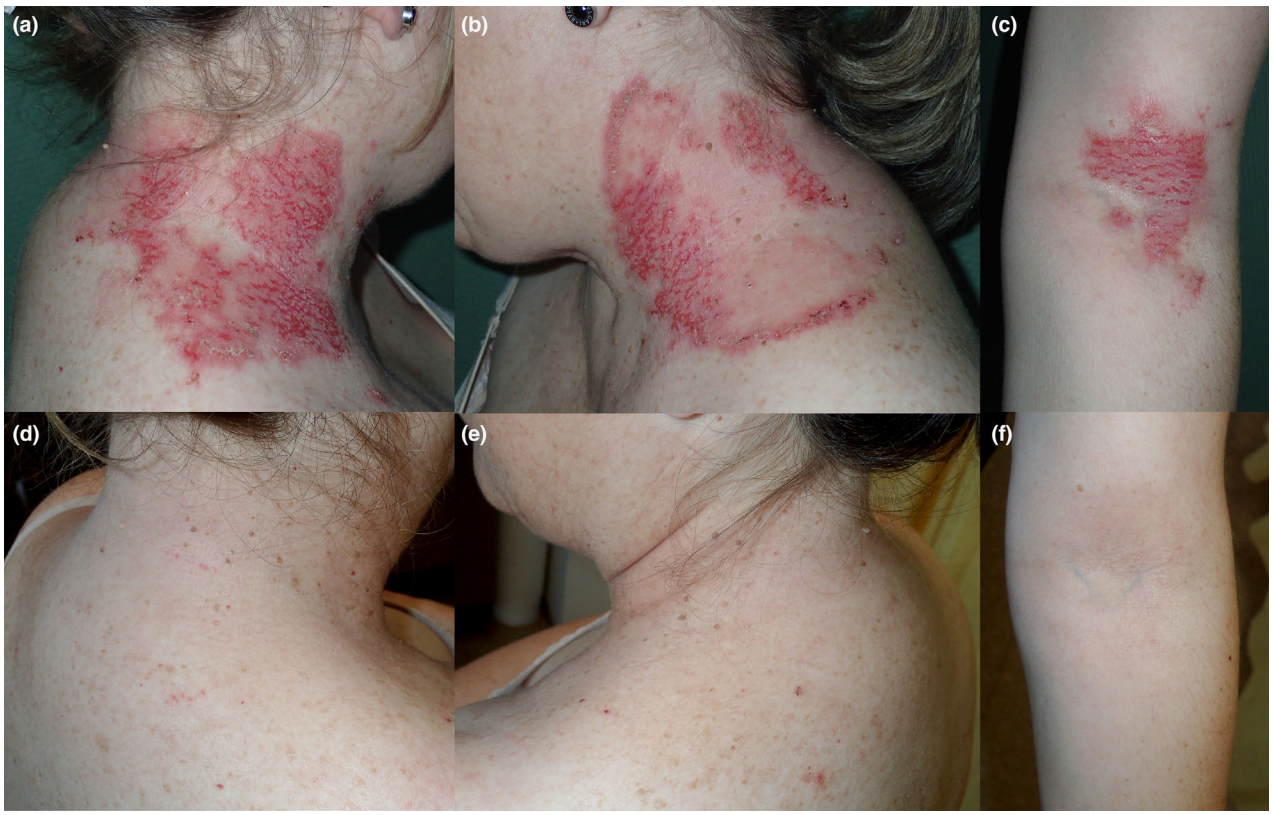

Figure 1 (a–c) Erythematous-scaly plaques on both cervical regions and left arm before treatment with apremilast. (d–f) Successful results after 6 months of treatment

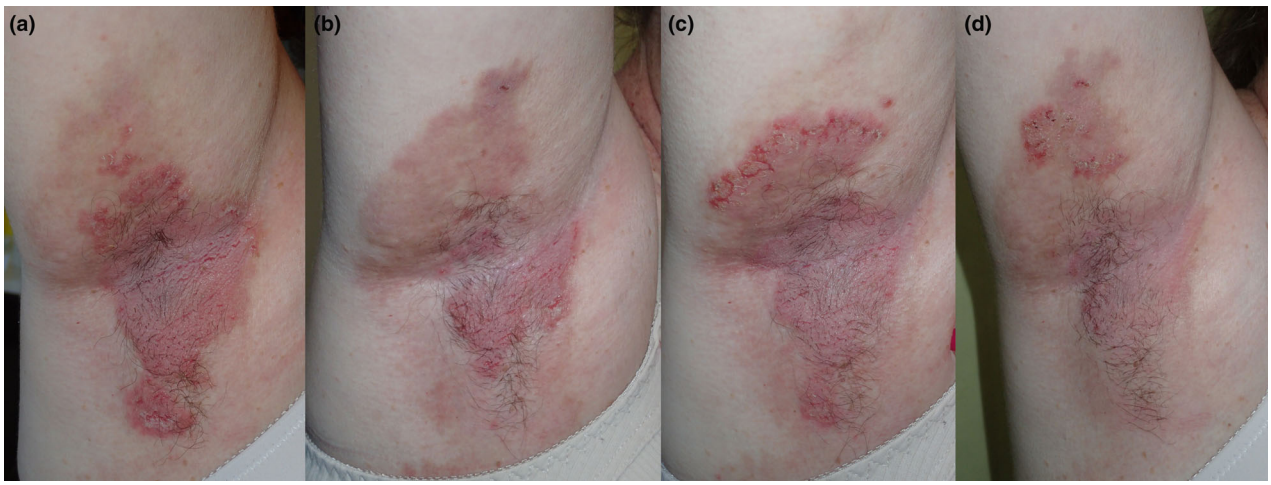

Figure 2 (a) Erythematous-scaly plaques in both armpits before treatment with apremilast. (b) Results after 4 months of treatment. (c) New flare-up just presented on both axillary regions after 6 months of apremilast 30 mg twice daily. (d) Improvement after the addition of a single session of botulinum toxin-A infiltrations

by inhibiting the NF-KB signaling pathway.[4] Recently, it has been postulated that high ROS levels may be the most important event in the development of HHD flare-ups.[5] In fact, in HHD keratinocytes, an increase in oxidative stress levels is observed but also a lower expression of the NOTCH1 and NRF2 genes responsible for cutaneous homeostasis.[4,5]

Few reports have been published on patients with refractory HHD who experienced marked improvement after treatment

Table 1 Summary of all Hailey–Hailey patients treated with apremilast reported in the literature

	Sex/Age	Previous treatments	Compromised areas	Treatment duration (months)	Response	Side effects	Relapses
Di Altobrando[2]	W/68	Tc, Tab, Oab, Mt, El	Axillary and lumbar	7[a]	PR	No	Yes
Julie Kieffer *et al*[3]							
1	W/50	Tc, Oav, Mt, Cd, El	Axillary and lumbar	7[a]	PR	No	Yes
2	W/60	Tc, Tt, Bt, Cd, El, Oav, Oab	Axillary, submammary, abdominal, inguinal, neck and back	6	PR	Diarrhea	No
3	W/50	Tc, Tt, Oab, Oav, Bt, El, Mt	Axillary, abdominal, neck and back	6	PR	No	No
4	M/50	Tc	Inguinal fold	10[b]	PR	Myalgia and diarrhea	Yes
Riquelme-Mc Loughlin *et al*[6]							
1	W/58	Ac, Tc, Tab, Tpp, Td, Ox, Da, Mi, Na	Not mentioned/(BSA 6%)	8	NI	Dyspepsia, GRD	–
2	W/54	Da, Mi, Do, Tpp, Ox, Oc, Az, Mt, Tc, Tab, Na	Not mentioned/(BSA 10%)	7	NI	No	–
3	V/50	Do, Co2, Oab, Ox, Tc, Tpp, Mi, Tab, Na.	Not mentioned/(BSA 5%)	10	NI	No	–
4	V/36	Tc, Oc, Do, Tab, Na	Not mentioned/(BSA 4%)	3	NI	No	–
5	W/55	Tc, Oc, Tt, Td, Ox, Oab, Na	Not mentioned/(BSA 5%)	Not tolerated	NT	Diarrhea and nausea	–

Ac, acitretin; Az, azathioprine; Bt, botulinum toxin-A injections; Cd, carbon dioxide laser; CO2, CO2 laser; CR, complete response; Da, dapsone; Do, doxycycline; El, erbium laser; GRD, gastroesophageal reflux disease; Mi, minocycline; Mt, methotrexate; Na, naltrexone; NI, no improvement; NT, not tolerated; Oab, oral antibiotics; Oav, oral antivirals; Oc, oral corticosteroids; Ox, oxybytynin; Tab, topical antibiotics; Tc, topical corticosteroids; Td, topical diclofenac; Tpp, topical potassium permanganate; Tt, topical tacrolimus; PR, partial response.

[a]After seven months of treatment with apremilast, she had a familial stress event and decided to stop the treatment. Her lesions became worse so apremilast was reintroduced with success.

[b]This patient decreased the apremilast dose to 30 mg once daily due to a digestive intolerance. His lesions became worse so his prescription was reverted to 30 mg twice a day along with probiotics.

with apremilast,[2,3] however, it is not always successful. This lack of response has been noted in other series such as Riquelme-Mc Loughlin et al.[6] and question the magnitude of the positive results seen to date (Table 1). Clinical response to apremilast may be limited to those locations where sweating is a well-known aggravating factor, hence the importance of complementing the treatment with other rescue therapies.[7] In our case, the neck and antecubital fossa lesions disappeared quickly after administration of apremilast, while the axillary patches showed an initial improvement, but underwent a subsequent relapse during the summer. As a result, additional treatment with BoNT infiltrations was added and led to the resolution of the lesions after a single session. The combined use of both therapies could have a synergistic effect that helps to better control the disease as occurred in our case.

In conclusion, apremilast is proposed as an alternative treatment in patients with severe and refractory HHD. During treatment, flare-ups may appear, especially in wet areas. Therefore, we suggest the combined use of apremilast with BoNT infiltrations as rescue treatment for lesions located in skin folds with excessive sweating activity.

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