protein levels in D-PsoR lesional skin (Figure 1b) in comparison to nonlesional skin (Figure 1c).

IL-26 is a signature Th17 cytokine, and its expression is regulated by IL-23A. It has been reported that IL-26 gene expression is increased in AD and Pso compared with HS.[6] We found decreased IL-26 levels in both lesional and nonlesional skin of patients with D-PsoR. Furthermore, IL-17A levels did not show any statistical differences in the three analysed groups. Psoriasiform plaques in the D-PsoR cohort showed decreased levels of IL-4 compared with nonlesional skin. Our findings highlighted a marked increase of IL-23A level in lesional skin of the patients in the D-PsoR group, thus suggesting the activation of the Th17 pathway. We also found a high expression of IL-23A in these patients compared with the Pso group.

IL-23A is a heterodimer proinflammatory cytokine mainly secreted by activated macrophages and dendritic cells. The outcome of dupilumab treatment argues for Th2-mediated pathogenesis in AD, but inflammatory pathways modulated by this drug extend to the IL-23A/Th17/Th22 axes, perhaps mediated by the effects of IL-4 receptor blockade in cutaneous dendritic cells.[1] Moreover, the IL-4 level was lower in lesional skin compared with nonlesional skin of the patients with D-PsoR. This result could be due to the compensatory switch from the Th2 to the IL-23A/Th17 axis in the psoriasiform plaques. Both Pso and AD are diseases in which the understanding of the inflammatory pathways has led to successful therapeutic developments.[1] Immunological mechanisms overlap between Pso and AD; thus, some treatment approaches may be common across the disease spectrum. Although this is a study conducted on a small number of patients, we found statistical significance in the data. Therefore, our results could suggest that IL-23A might be a therapeutic target for patients with D-PsoR or overlapping patterns of the two diseases.

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Noninvasive assessment of cytokine and antimicrobial peptide levels in hidradenitis suppurativa using transdermal analysis patches

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Dear Editor, Most of the currently available cytokine and antimicrobial peptide (AMP) expression data from hidradenitis suppurativa (HS) lesions have been obtained through painful, invasive sampling techniques such as biopsies.[1] In contrast, a Transdermal Analysis Patch (TAP, FibroTx, Tallinn, Estonia) captures and measures biomarkers at the skin surface and as such represents a novel, noninvasive and patient-friendly diagnostic tool for skin biomarker detection. The aim of this study was to measure the levels of several cytokines and AMPs in both lesional and uninvolved skin of patients with HS and site-matched skin of controls using TAPs.

Twenty patients with HS and 10 healthy control participants were included. TAPs contained capturing antibodies for interleukin (IL)-1α, IL-1RA, IL-8, IL-12, IL-17A, IL-23p19, C-C motif chemokine ligand 27, kallikrein-related peptidase-5, human β-defensin (hBD)-1, hBD-2, hBD-3, hBD-4 and a negative and IgG control. The patches were applied on inflamed lesions in the axilla and groin, on associated uninvolved skin, and on identical sites in controls.[2] TAPs remained in place for 20 min, and were stored at −20 °C until further analysis by spot enzyme-linked immunosorbent assay (ELISA).[3] Using GraphPad Prism (v. 8), differences were analysed with Wilcoxon signed-rank tests or Mann–Whitney U-tests. P-values $\leq 0{\cdot}05$ were considered significant. Approval was granted by the institutional review board of the Erasmus University Medical Center (MEC-2017-1126).

Eighty per cent (16 of 20) of the included patients with HS were female, 12 had Hurley stage II or III and 13 patients were current smokers, the mean body mass index (BMI) was $30{\cdot}7 \pm 7{\cdot}12$. Eighty per cent (8 of 10) of controls were female and none were current smokers, with a mean BMI of $23{\cdot}1 \pm 3{\cdot}3$.

Significantly lower concentrations of IL-1α were found in HS lesional axilla skin compared with uninvolved skin ($P = 0{\cdot}016$); see Table 1 for fold changes (absolute levels are available on request). Lesional axillary and uninvolved upper arm skin in patients with HS showed significantly higher concentrations of IL-17A than in controls (respectively, $P = 0{\cdot}010$ and $P = 0{\cdot}009$). In patients with HS and controls lower concentrations of IL-23p19 were found in axilla and groin skin compared with uninvolved skin. Levels of hBD-2 were significantly increased in lesional axilla and groin compared with uninvolved sites, respectively, $P < 0{\cdot}001$ and $P < 0{\cdot}001$. Significantly different concentrations of hBD-1, hBD-2 and hBD-3 were seen between uninvolved skin of patients with HS and identical sites in controls.

The IL-1 pathway is known to be activated in HS, yet our study showed decreased levels of IL-1α in HS lesional skin compared with uninvolved skin. Lower IL-1α levels in lesional HS skin could reflect intracellular location and consumption of IL-1α at sites of inflammation.[4,5] However, further investigation is needed to understand the complex regulation of IL-1 in the skin and in HS.

In contrast to the elevated concentrations of hBD-2 and hBD-3 in HS lesional skin, the level of hBD-1 was decreased compared with controls. Lower levels of hBD-1 in lesional tissue have been described previously by Hotz *et al.*[6] In contrast to hBD-2 and hBD-3, expression of hBD-1 is not induced by inflammatory stimuli such as tumour necrosis factor-α, IL-1β and interferon-γ.[7] The mechanisms behind the decreased levels of hBD-1 in HS pathogenesis remain elusive. The significantly higher levels of hBD-2 in uninvolved HS skin compared with identical sites in controls is suggestive for an activated innate immune system in the uninvolved skin in patients with HS.

Relatively high concentrations of IL-23p19 were found in all samples and no significant differences were seen between patients with HS and controls. The detection of increased levels of IL-23p19 in lesional HS biopsies, which capture both epidermis and dermis, and the lack of differences in lesional skin compared with controls when measured with TAPs, might indicate that IL-23 secreted by keratinocytes plays a lesser role in HS pathogenesis than IL-23 released by dermal dendritic cells.[1]

The detection of biomarkers from the topmost layers of the skin could be seen as a limitation in HS as the deep dermal infiltrate, characteristic of the disease, is probably not fully captured by a TAP. Nevertheless, keratinocytes are active players in HS inflammation and assessing keratinocyte-related inflammatory mediators in a noninvasive manner could provide new insights into their role in the pathogenesis of HS.

In conclusion, this is the first study assessing the expression of cytokines and AMPs using TAPs in patients with HS. We showed that TAPs can be used effectively to evaluate a wide range of HS-associated biomarkers in the skin. Additionally, the noninvasive, patient-friendly nature of this technique could prove to be of specific value for monitoring the inflammatory state of the skin over time both in clinical trials and daily practice. The results found in this study support a role for anti-IL-17A in the treatment of HS, but raise questions on the benefit of anti-IL-1α. Overall, our results confirm previously published data obtained with invasive techniques and highlight the role of the epidermis and subclinical inflammation in HS pathogenesis.

Table 1 Fold changes (FC) of inflammatory cytokine and antimicrobial peptides measured with transdermal analysis patches, showing significant results after Benjamini–Hochberg correction for multiple testing

	HS lesional axilla vs. HS uninvolved upper arm		HS lesional axilla vs. HC axilla		HS uninvolved upper arm vs. HC upper arm		HS lesional groin vs. HS uninvolved thigh		HS lesional groin vs. HC groin		HS uninvolved thigh vs. HC thigh	
	FC	P-value	FC	P-value	FC	P-value	FC	P-value	FC	P-value	FC	P-value
IL-1α	0·53 ↓	**0·017**[b]	3·32	ns	0·99	ns	0·53	ns	1·02	ns	1·52	ns
IL-1RA	0·48	ns	3·32 ↑	**0·027**	0·70	ns	1·95	ns	15·20 ↑	**0·007**	1·12	ns
IL-8	20·91 ↑[a]	**0·003**[b]	20·91 ↑[a]	**0·007**	ND	–	11·01 ↑[a]	**0·003**[c]	11·01 ↑[a]	**0·009**	ND	–
IL-12	ND	–	ND	–	ND	–	ND	–	ND	–	ND	–
IL-17A	1·19	ns	16·59	0·011	9·22 ↑	**0·010**	0·99	ns	2·25	ns	2·00	ns
IL-23p19	0·69	ns	1·16	ns	1·18	ns	0·70 ↓	**0·027**	0·92	ns	1·06	ns
CCL-27	0·57	ns	1·00	ns	0·71	ns	1·00	ns	1·00	ns	1·00	ns
KLK-5	1·47	ns	3·04	ns	1·85	ns	1·42	ns	2·80	ns	0·95	ns
hBD-1	0·53 ↓	**0·006**	0·50 ↓	**0·015**	0·72	ns	1·34	ns	1·03	ns	0·53 ↓	**0·024**
hBD-2	5·43 ↑	**0·001**	9·14 ↑	**0·022**	1·68 ↑	**0·010**	4·24 ↑	**< 0·001**[d]	8·30 ↑	**< 0·001**	1·96 ↑	**0·011**
hBD-3	1·10	ns	1·24	ns	1·00	ns	1·09	ns	1·26 ↑	ns	1·06	ns
hBD-4	ND	–	ND	–	ND	–	ND	–	ND	–	ND	–

CCL-27, C-C motif chemokine ligand 27; hBD, human β-defensin; HC, healthy control; HS, hidradenitis suppurativa; IL, interleukin; KLK, kallikrein-related peptidase; ND, not detected in both groups; ns, not significant; **bold**, significant ($P \leq 0{\cdot}05$). [a]Analysed using half of the lower limit of detection for one of the groups where data was under limit of detection; [b]missing, n = 3; [c]missing, n = 2; [d]missing, n = 1.

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Transient response to nivolumab and relapse after infliximab in a patient with primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma

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Dear Editor, Primary cutaneous $CD8^+$ aggressive epidermotropic T-cell lymphoma ($CD8^+$ AECTCL) is a very rare subtype of cutaneous T-cell lymphoma. The frequency is less than 1% of all primary cutaneous lymphomas and prognosis is poor, with a 5-year disease-specific survival rate of 31%.[1] Because of the rarity of this entity, there are no evidence-based treatment options.

We report the case of a 70-year-old female patient who presented with a red plaque with central ulceration on the left shin rapidly developing in 2 weeks. Skin biopsy revealed atypical lymphoid cells in the epidermis and dermis with atypical mitoses (Figure 1a). Immunohistochemical stains showed reactivity with CD3, CD8 (Figure 1b), TIA-1 and programmed cell death 1 ligand 1, with weak reactivity for programmed cell death protein 1 (PD-1) expression. CD2, CD4, CD20, CD30 and CD56 were negative. Cranial magnetic resonance imaging (MRI) and computed tomography (CT) scan of neck, thorax and abdomen showed no evidence of metastases. Bone marrow biopsy revealed no infiltration with lymphoma cells, and blood count was normal. Primary cutaneous $CD8^+$ aggressive epidermotropic T-cell lymphoma was diagnosed.

Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) every 21 days was started. After six cycles of chemotherapy the plaque was clearly regressive, and consolidating radiotherapy of the left lower leg was started. Still on radiotherapy, the patient developed disseminated, well demarcated erythematous patches and plaques, many with necrotic ulcerations, involving all extremities and trunk (Figure 1c), and ulceration on the hard palate. Cranial MRI, CT scan and fluorescence-activated cell sorting analysis ruled out extracutaneous manifestation. Photochemotherapy with psoralen plus ultraviolet A and treatment with topical corticosteroids class IV were initiated without significant improvement. Due to progression, therapy was changed to an anti-PD-1 antibody. After five infusions of nivolumab (2 mg kg^{-1}) the patient experienced near complete remission of all lesions (Figure 1d). Only a singular new erythematous plaque with no ulceration appeared on the trunk during treatment. An additional skin biopsy was performed, which showed similar findings to the initial diagnostic specimen. After seven infusions of nivolumab she developed autoimmune diarrhoea grade 2 (Common Terminology Criteria for Adverse Events). Therapy was paused and treatment with prednisolone at 1 mg kg^{-1} orally was started and slowly tapered. Owing to persistent symptoms, one infusion with a tumour necrosis factor (TNF)-α inhibitor (infliximab) 5 mg kg^{-1} was applied. Diarrhoea improved and nivolumab was restarted 1 month after cessation. However, in the following 3 months, new disseminated erythematous and ulcerated plaques appeared and the patient developed a painful massive swelling in the preauricular region. MRI showed a mass in the parotid lodge infiltrating the masseter muscle. Treatment was switched to total body irradiation. However, the patient's condition deteriorated rapidly and she died from sepsis 14 months after diagnosis.

Checkpoint inhibitors play an increasing role in the treatment of patients with solid and haematological malignancies. More recent studies evaluated the safety and efficacy of anti-PD-1 antibodies in patients with cutaneous T-cell lymphomas, including