

treatment was required to maintain response and skin atrophy has been reported even when lower concentration was used.<sup>2</sup>

Trichoscopy findings of the eyebrows in FFA patients most commonly show non-inflammatory and non-scarring features in contrast to scarring alopecia on the affected scalp.<sup>8</sup> Pretreatment trichoscopy enables better patient selection for those who might benefit from prostaglandin analogue given the varied treatment response. Analysis of eyebrow histopathology in FFA had demonstrated the association of eyebrow regrowth with preservation of sebaceous glands. Destruction of sebaceous glands is considered the earliest sign of scarring alopecia.<sup>9</sup> The diverse clinical features and treatment response could be due to the involvement of non-androgen-dependent follicular units in eyebrow disease. Reports of treatment response to anti-androgen in some patients with FFA support the hypothesis that the affected hair follicular unit with less androgen influence has less severe disease activity and scarring.<sup>10</sup>

The exact mechanism of action of prostaglandin analogue in promoting eyebrow regrowth in FFA is unclear but it serves as a good complementary role to the other treatment. It is likely that favourable response to treatment could only be achieved in cases where fulminant scarring of the hair follicular unit has not occurred. Although skin irritation and dyspigmentation are common adverse effects, none of our patients had experienced it and patients 1 and 2 were keen to continue with the treatment. Favourable outcomes in the premenopausal patients in this series might have occurred by chance due to a limited sized study. Further controlled and randomized studies could provide more robust evidence in support of its role for treatment of this specific area involved in FFA and possibly in the main areas on the scalp.

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### Patient consent

The patients in this manuscript have given written informed consent to publication of their case details.

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## Evidence for different immune signatures and sensitization patterns in sub-Saharan African vs. Central European atopic dermatitis patients

To the Editor

Atopic dermatitis (AD) has only recently been recognized as a major public health issue in sub-Saharan Africa (sSA).<sup>1,2</sup> In contrast to Afro-American or South African AD patients, data on clinical and immune-related features on sSA AD patients are scarce.<sup>1–3</sup> In this study, we wanted to explore immune phenotypes of sSA vs. Central European (CE) AD patients and put them into context to environmental influences by assessing sensitization patterns. The study was approved by the local ethics committees (EK 2016-00301). We collected serum specimens of 10 AD outpatients and 10 age- and sex-matched healthy controls (HC) both in Moshi (Regional Dermatology Training Centre), Tanzania, and in Zurich (University Hospital Zurich), Switzerland. SCORAD was used to assess AD severity. Patient characteristics and self-reported allergic comorbidities are shown in Table 1.

Total IgE levels were significantly higher in Swiss compared with Tanzanian AD patients (Fig. 1a). Measurements of specific IgE

**Table 1** Patient characteristics

| Patient characteristics      |                                     |                          |              |              |
|------------------------------|-------------------------------------|--------------------------|--------------|--------------|
|                              | AD TZ                               | AD CH                    | HC TZ        | HC CH        |
| Sex                          | F: 3<br>M: 7                        | F: 3<br>M: 7             | F: 5<br>M: 5 | F: 5<br>M: 5 |
| Age (mean years $\pm$ SD)    | 43 $\pm$ 12                         | 42 $\pm$ 14              | 33 $\pm$ 14  | 31 $\pm$ 8   |
| Disease severity†            | Mild: 1<br>Moderate: 3<br>Severe: 6 | Moderate: 3<br>Severe: 7 | —            | —            |
| Allergic rhinoconjunctivitis | 8/10                                | 7/10                     | 0/10         | 2/10         |
| Allergic asthma              | —                                   | 4/10                     | —            | —            |
| Food allergies               | —                                   | —                        | —            | —            |

AD, atopic dermatitis; F, female; HC, healthy controls; M, male; SD, standard deviation.

†Disease severity, assessed by SCORAD; mild: SCORAD 0–19; moderate: 20–34; severe: >35. Data on allergic comorbidities are based on clinical history taking.

against a wide range of antigens by multiplex allergen-specific IgE testing (Macro Array Diagnostics GmbH, Vienna, Austria) revealed very different sensitization patterns in Swiss and Tanzanian patients. Specific IgE against *Malassezia* spp antigens was elevated in 9/10 Swiss, but only 1/10 Tanzanian AD patients (Fig. 1b). These results were confirmed by ImmunoCAP assay (m227, data not shown). Most AD patients (7/10 Swiss and 6/10 Tanzanian) were highly sensitized to house dust mite antigens (Fig. 1c). Elevated IgE levels against storage mite and cockroach antigens and certain seafood antigens were present in Tanzanian AD patients only (Fig. 1d,e). Parasitic helminth infections could be an additional environmental factor influencing AD development, IgE levels and tropomyosin sensitization in sSA. A screening for parasite-specific IgG antibodies using a standard enzyme-linked immunosorbent assay was negative for all patients and HC (data not shown). Analysis of inflammation-associated proteins by high-throughput proteomics (Inflammation panel, Olink, Uppsala, Sweden) revealed major differences between Tanzanian and Swiss AD patients (Fig. 1f). Tanzanian AD patients had higher serum levels of pro-inflammatory Th1/Th17 cytokines/chemokines (among others IL-17A, IL-17C, CCL19, CXCL5). In contrast, levels of certain mediators interfering with apoptotic and growth pathways were lower in the Tanzanian AD cohort.

The findings from this exploratory study indicate that AD patients from sSA and CE have vastly different IgE sensitization patterns and distinct serological immune signatures. One of the most surprising results was the lack of *Malassezia* sensitization in Tanzanian AD patients. *Malassezia furfur* has been associated with AD in Caucasians.<sup>4,5</sup> Although previously identified as a dominant skin-colonizing yeast subspecies in Tanzanians,<sup>6</sup> the role of *Malassezia furfur* in African AD has not been addressed yet. It thus is conceivable that either skin mycobiome differences (due to major temperature/humidity differences) or diverse cutaneous immune responses<sup>7</sup> contribute to the observed absence of IgE sensitization. The sensitization to house dust and storage mites, cockroach and seafood antigens observed in Tanzanian AD patients strongly suggests tropomyosin cross-reactivity.<sup>8</sup> The question as to the antigenic source and way of sensitization

remains to be elucidated. The distinct pro-inflammatory, Th1/Th17 immune signature in sSA AD patients points towards an immunophenotype, that is not only different from Caucasian, but also Asian and Afro-American AD patients.<sup>3</sup>

In conclusion, our exploratory study points towards considerable endo-/phenotypical varieties between sSA and CE AD and constitutes the basis to further explore these features, their underlying mechanisms and potential therapeutic implications.

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### Conflict of interest

The authors state no conflict of interest regarding this project: Dr. Lang, Dr. Masenga, Dr. Kaderbhai, Dr. Li, Dr. Tan, Dr. Heider, Dr. Guttman-Yassky, Dr. Grimm, Dr. Schmid-Grendelmeier and Dr. Brüggen have nothing to disclose.

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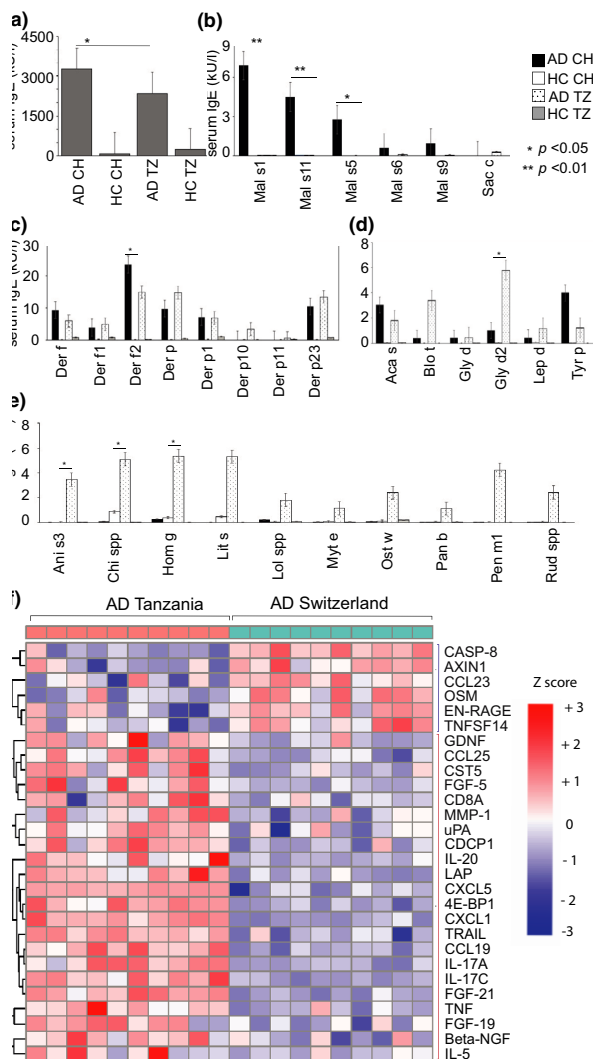


**Figure 1** Sensitization patterns in Tanzanian and Swiss atopic dermatitis (AD). (a) Bar charts representing the total IgE levels (kU/L)  $\pm$  SD in Swiss and Tanzanian AD patients and healthy controls (HC) ( $n = 10$  per group). (b–e) Bar charts representing the specific IgE levels (kU/L)  $\pm$  SD against (b) yeast antigens, (c) house dust mite antigens, (d) food mite antigens and (e) seafood antigens. \* $P < 0.05$ ; \*\* $P < 0.01$ . (f) Heat map depicting proteins significantly up- and downregulated in AD patient sera (Tanzania on the left-hand side, Switzerland on the right-hand side). Protein expression in both groups is normalized to their respective Tanzanian and Swiss HC. The blue line on the right of the heat map indicates lower expression, and the red line indicates higher expression in comparison with Tanzanian compared with Swiss AD.

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## Characteristic pathological features of keratinocyte death in a case of Stevens–Johnson syndrome manifested by an immune checkpoint inhibitor

Dear Editor

A 71-year-old female was treated with pembrolizumab for lung cancer three months prior. However, pembrolizumab was discontinued, and prednisolone 50 mg/day and trimethoprim/sulfamethoxazole were started for immune checkpoint inhibitor (ICI)-induced interstitial pneumonia a month prior. She developed painful reddish erythema and blisters on palms and soles, sporadic erythema on trunk and mucosal erosion when PSL was tapered to 27.5 mg/day (Fig. 1a–d). The skin biopsy showed keratinocyte death, which was dominant in basal layer, and remarkable interface change (Fig. 1e,f). Her symptoms improved with an increase in prednisolone to 50 mg/day. The stimulation index (S.I.) of lymphocyte transformation test (LTT) with trimethoprim/sulfamethoxazole was remarkably high at 13.6 and decreased to 1.8 six months after the last administration of pembrolizumab. This significant decrease led us to a final diagnosis of trimethoprim/sulfamethoxazole-induced SJS enhanced by pembrolizumab.

Histopathological findings which were different from typical SJS and the results of LTT led to concerns that pembrolizumab affected the skin immunological response. Therefore, we focused on the type of keratinocyte death and infiltrating cells to clarify the characteristics of ICI-related SJS. Immunohistochemical analysis revealed CD8+ lymphocytes infiltrated the dermal–epidermal