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\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0,0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patienten mit aktiver PsA.[4]

1. Aktuelle Fachinformation TREMFYA®. **2.** Reich K et al. Lancet. 2019;394(10201):831–839. **3.** Reich K et al. Br J Dermatol. 2021 Jun 9. doi: 10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

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Clinical Letter

Oral lesions in keratosis lichenoides chronica – a distinct histopathological criterion

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Dear Editors,

although keratosis lichenoides chronica (KLC) presents a distinctive morphology, it is not always known in its own right due to its rarity - only about 70 cases have been published to date [1–3] - and an inconsistent presentation of its diagnostic features.

In the course of a comprehensive review of the literature, Almut Böer used 66 described cases to highlight a characteristic combination of clinical and histopathological findings (Table 1, cental column), which was present in all unambiguous cases and was not compatible with any other dermatosis [4]. She suggested that these criteria should be reviewed on the basis of subsequent case reports and supplemented as necessary [4].

The distinctive lesions of KLC are reddish-livid keratotic papules sometimes atrophic with tiny erosions or crusts in their center that coalesce into a striated linear, at times reticular or arcuate pattern. They are predominantly located on the extremities. On the face, the lesions resemble seborrheic

Table 1 Histological criteria for differential diagnosis.

Criterion	Lichen ruber planus [12]	Keratosis lichenoides chronica [4]	Case report
Parakeratosis	Skin: rare, without neutrophils Oral: more common	Staggered with remnants of neutrophils	Skin focal, with neutrophils, intracorneal pustules Oral: discrete, with neutrophilic granulocytes
Hypergranulosis Hypogranulosis	Continuous, focally accentuated hypergranulosis; hypogranulosis in atrophic zones	Wedge-shaped hypergranulosis sometimes in acanthosis zones absent parakeratosis zones	Skin: wedge-shaped hypergranulosis in zones of acanthosis Oral: (absent) Skin: hypogranulosis below zones of parakeratosis Oral: linear fragmented stratum granulare
Atrophy	atrophic lesions, often in later stages (31.3 %, n = 100) [12]	areas of atrophy, sometimes in center of lesion or around erosions, alternating with areas of acanthois or parakeratosis	Skin: in the center of lesions Oral: –
Acanthosis	Hypertrophic, compact, sawtooth-shaped	Uneven acanthosis in foci; when covered by parakeratosis and remnants of neutrophils staggered between zones of orthokeratosis it correlates with the keratotic papules	Skin: variable, more pronounced in the periphery of lesion Oral: *pronounced acanthopapillomatosis*
Basal hydropic vacuolar degeneration	Focal (10 %) continuous (90 %, n = 145)	focal	Skin: discrete in the center of the lesion Oral: focally accentuated
Necrotic keratinocytes	Rare	Numerous, sometimes in clusters, in surface epidermis and infundibular epidermis, especially in the lower part of it	Skin: sparse necrotic keratinocytes Oral: some necrotic epithelial cells in upper epithelial areas
Dyskeratoses	Occasional	many [5]	Skin: – Oral: some, punctual near zones of erosion
Keratin (Civatte) bodies	several (in lower part of epidermis and in stratum papillare), (65 %, n = 94), of IgM type (86.2 %, n = 63)	Skin: some [2, 3, 6]	Skin: isolated Oral: several, basally located
Infiltrate	Band-like or patchy, lymphocytic (84.5 %, n = 120)	Patchy, lichenoid, lymphocytic, often centered around infundibula and acrosyringia; clinical correlate for discrete papules	Skin: lichenoid, lymphocytic, often centered around infundibula and acrosyringia Oral: broad banded, centered around glandular end pieces of salivary palatine glands

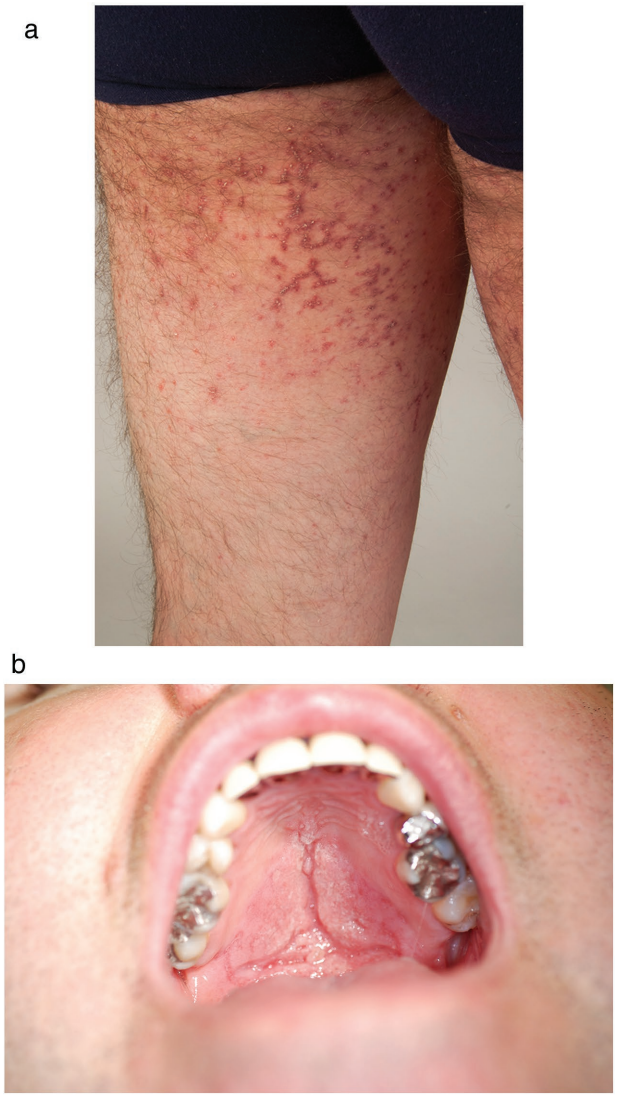

Figure 1 Left thigh: red-livid keratotic papules in linear and reticular array (a). Soft palate: white partially reticular or patchy plaques, surrounded by a markedly erythematous margin (b).

eczema. Less frequently affected are the trunk, genitalia, and eyes. In 25 % [4] to 50 % [3] of cases, involvement of the oral mucosa also occurs, described as aphthoid [2, 5], erosive [1, 5] or ulcerative [3, 5–7]. Their precise appearance was not listed under the above criteria [4].

We want to confirm that a diagnosis of KLC can be made conclusively based on the aforementioned criteria [4] and to point out a specific oral mucosal involvement.

A 43-year-old male patient presented for diagnostic assessment of conspicuous lesions existing since puberty. Previous local treatments with cream-PUVA, topical glucocorticosteroids, tacrolimus and calcipotriol based on a suspected diagnosis of lichen planus were unsuccessful. In addition, the patient suffered a moderate impairment of intelligence due to early childhood brain damage.

On both inner thighs and transitioning to dorsal areas (Figure 1a), red, keratotic papules were present in a linear, arcuate and reticular, partially confluent configuration. The face impressed with erythema, with single vascular dilatations and discrete scaling. The oral cavity displayed white, striped and reticular, flat plaques at the soft palate, interspersed with punctate red macules (Figure 1b). On the buccal mucosa of both cheeks, an alternating patchy and reticular whitish pattern could be seen. Clinical signs of oral candidiasis or lupus erythematosus were not present. Dryness of mouth or other complaints were denied.

Three skin biopsies showed staggered parakeratosis and an intraconreal accumulation of neutrophilic granulocytes (Figure 2a), alternating with areas of extended rete ridges, hypergranulosis, orthohyperkeratosis, and occasional atrophic centers (Figure 2b). There was a patchy lichenoid interface dermaitis and a lichenoid infiltrate centered around infundibula and acrosyringia. Some superficial demal vessels were ectatic.

A mucosal biopsy from the soft palate showed massive acanthopapillomatosis (Figure 3a) without hypergranulosis, a discrete parakeratosis and neutrophils (Figure 3b), seen mainly on narrowed epithelial areas above the upward extending stratum papillare. The latter displayed abundant

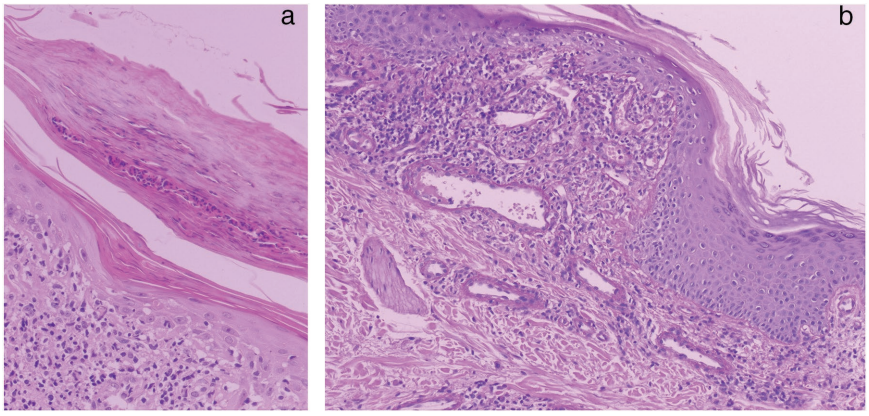

Figure 2 Parakeratosis with foci of neutrophils (hematoxylin-eosin stain original magnification x 600) (a). Central atrophy and marginal hypergranulosis and irregular acanthosis as well as discrete vacuolic degeneration of the basal cell layer. In the papillary stratum ectatic vessels filled with red blood cells; perivascular infiltrate in the upper corium (Periodic acid-Schiff reaction [PAS] original magnification x 200) (b).

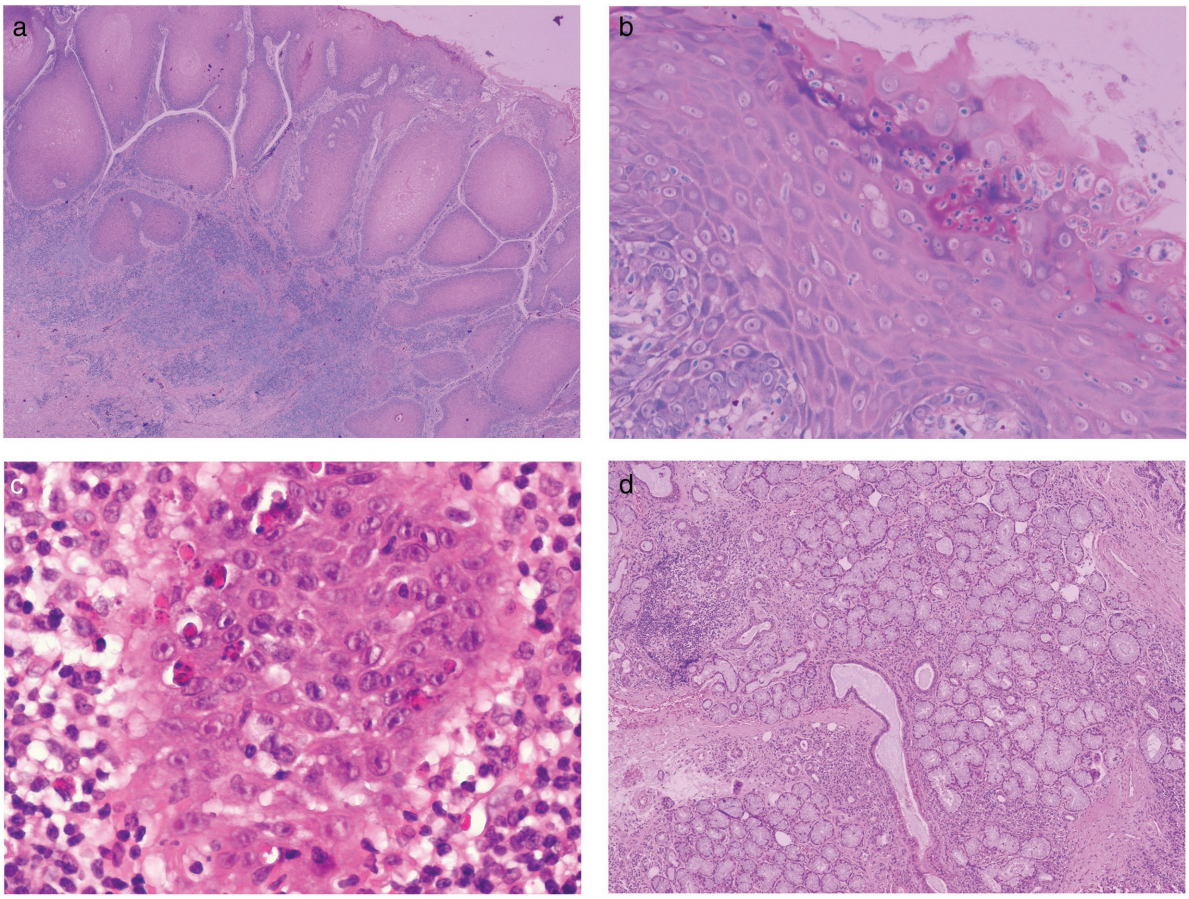

Figure 3 Marked acanthosis and papillomatosis In the stratum papillare perivascular lymphocytic infiltrate; in the lamina propria dense and band-like lymphocytic infiltrate (PAS, original magnification x 20) (a). Accumulation of neutrophils in the upper epithelial layer (PAS original magnification x 600) (b). Single apoptotic cells with pyknotic nuclei (hematoxylin-eosin stain x original magnification x 400) (c). Infiltrate around palatine glands (PAS original magnification x 40) (d).

ectatic vessels. Focally, hydropic vacuolar degeneration of the basal cell layer and basally located keratin (Civatte) bodies were observed (Figure 3c). Except for acanthosis and isolated dyskeratotic cells, there were no cytologic or architectural signs of malignant intraepithelial neoplasia.

PAS staining revealed focal spores in the stratum corneum. By immunohistochemistry, p16 was found intracytoplasmically to a minor extent and partly also intranuclearly, in each case in the periphery of acanthotic formations, but without block-like expression patterns. The proliferation marker Ki-67 showed linear expression in the basal cell layer, which is typical for normal epithelium. *Candida albicans* was detected in the oral cavity by mycological culture. Serologically, no antinuclear antibodies were present.

Based on the lesions, histologic findings, and published criteria [4] we made a diagnosis of KLC.

Since no subjective symptoms were present and no reliably effective therapy is known [1–5, 7] - a circumstance partially confirmed by the lack of success of the therapies previously administered to our patient - we refrained from further treatment attempts.

The fact that the diagnosis was made many years after the onset of the disease may be due to the low awareness of the dermatosis, its peculiarities, and the only recent elaboration and proposal of good distinctive criteria [4]. In order to diagnose KLC with certainty, the typical clinical as well as histologic signs should be present, to avoid wrongly classifying other, imprecisely clarified clinical manifestations as KLC [8, 9]. Should those wrongly classified dermatoses then respond well to glucocorticoids, it might raise false hopes of an easy treatment for KLC [8, 9].

Based on our observations and our review of the literature, we believe that lesions on the oral mucosa represent another helpful feature for differential diagnosis of KLC. Clinically, the plaques on the soft palate with their thickened striated reticular surface can be distinguished somewhat from plaque-like lichen mucosae due to their localization, as the latter affects the dorsum of the tongue and the buccal

mucosa rather than the margins of the tongue or the palate [10]. On buccal mucosa, they also differ from the more regular Wickham's streak of lichen mucosae with their alternating reticular and patchy pattern.

Histologically, we saw the following distinguishing features in the mucosa (Table 1): *(1)* KLC lacks hypergranulosis, which is considered a leading criterion for lichen mucosae; *(2)* the marked papillomatosis (Figure 3a) and accumulation of neutrophilic granulocytes (Figure 3b) are uncharacteristic of lichen mucosae; *(3)* the lymphocytic infiltrate concentrated at the glandular end pieces of the palatine glands (Figure 3d) would be unusual for lichen mucosae.

The keratin (Civatte) bodies (Figure 3c) oriented basally in the mucosal lesions could reflect apoptosis of epithelial cells as described in KLC [2, 3, 6, 11]. However, in our case, they are only occasionally found cutaneously. Additionally, since they occur in both lichen (ruber) planus [12] and KLC, and reportedly are more numerous and larger there [6], they would not be a sufficiently distinguishing feature. Meanwhile, the strikingly numerous ectatic vessels (Figure 2b) in the papillary body of mucosal and cutaneous lesions, although not explicitly emphasized in the respective publications, but shown in their illustrations [1–3, 5], could be an additional histologic feature of KLC.

Parakeratosis and an accumulation of neutrophils, but not the pronounced acanthopapillomatosis and the infiltrate penetrating deeply into the lamina propria, are also seen in oral candidiasis [13], although in that case the epithelial distribution of granulocytes would also be denser. There was no clinically manifest oral candidiasis, and previous antifungal therapies (due to repeated detection of *Candida albicans*) had not altered the clinical findings, so our findings comply with colonization rather than infection. There is no evidence for chronic mucocutaneous candidosis in KLC in the literature, and the patient lacked the often typical additional cutaneous or paronychial candidosis.

Because of the marked acanthosis of the mucosa, we wanted to exclude histologically various forms of a highly differentiated squamous cell carcinoma, even though there was no high clinical suspicion. Although a p16 stain did show some positive cells, the pattern was not typical for malignant processes but rather resembled benign oral hyperplasia [14]. In addition, the following clinical or histological criteria argued against a verrucous carcinoma, progressive verrucous leukoplakia (PVL), or stages of intraepithelial dysplasia: the absence of a verrucous or wavy whitish surface, the absence of involvement of the gingiva (as in PVL) or the tongue and floor of the mouth (as in squamous cell carcinoma), the absence of multifocal lesions, and, especially histologically, the absence of epithelial dysplasia.

Our conclusions: the existing criteria [4] are helpful for the reliable diagnosis of KLC and should allow more frequent and unambiguous diagnoses to be made. The changes to the oral mucosa may represent an additional criterion for differential diagnosis worth to be verified. A potential relevance of colonization or infection with Candida albicans should be investigated, while a premalignancy is unlikely.

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Conflict of interest

None.

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