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Paraneoplastic spongiotic dermatitis associated with progression to treatment-requiring chronic lymphocytic leukemia

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Running head: Spongiotic dermatitis in CLL

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A 74-year-old man presented with a three-month history of worsening, severely pruritic skin eruptions, accompanied by chills, fatigue, malaise, loss of appetite, and burning skin sensations. His medical history was significant for chronic lymphocytic leukemia (CLL), diagnosed in December 2022 at Binet stage A and initially managed with a watch-and-wait approach [1]. At diagnosis, leukocyte counts were 13.2 G/L with 61% lymphocytes, corresponding to an absolute lymphocyte count of 8.1 G/L. Immunophenotyping revealed a monoclonal B-cell population with a CLL-typical phenotype (CD19+, CD5+, CD23+, kappa light-chain restriction). Subsequent molecular and cytogenetic risk assessment showed mutated immunoglobulin heavy-chain variable region (IGHV) status with 92.0% identity to the germline sequence, wild-type TP53, no CLL-relevant aberrations by fluorescence in situ hybridization, including absence of del(17p), and normal serum β2-microglobulin, consistent with a favorable-risk profile. The longitudinal disease course is summarized in Figure 1.

Examination showed generalized erythroderma with widespread, partially confluent erythematous macules, succulent papules, and plaques involving the trunk and extremities as well as the face, scalp, and palms. On the upper arms, we observed infiltrated annular plaques. The scalp showed coarse, lamellar, whitish, firmly adherent scaling, and the palms exhibited dyshidrosis lamellosa. Nikolsky sign was negative, skin was xerotic without oozing or blistering (Figure 2A-C). Based on the clinical presentation, subacute cutaneous lupus erythematosus (SCLE) and Sweet syndrome were initially considered [2,3].

Prior dermatological treatment included topical methylprednisolone aceponate, systemic prednisolone, initially at 20 mg daily, escalated up to 60 mg followed by consecutive tapering, as well as additional dapsone 50 mg daily. Only partial short-term improvement was achieved, with rapid relapse upon dose reduction despite intensified topical and phototherapy-based dermatological management (Figure 2D-F).

Serological testing revealed negative antinuclear antibodies (ANA < 1:100) and negative extractable nuclear antigens (ENA). Further laboratory investigations showed a selective IgM deficiency, with serum IgM of 0.15 g/L, consistent with CLL-associated humoral immune dysregulation[4,5]. Screening for hepatitis B and C, HIV and tuberculosis was negative. Histopathological examination of an early skin biopsy from the lower back showed an urticarial reaction pattern with additional epidermal involvement and focal spongiosis (Figure 3A), consistent with an acute eczematous dermatitis but not indicative of lupus erythematosus. Focal immunoexpression of myxovirus resistance protein A (MxA), a type I interferon-inducible protein, was observed in focal epidermal and perivascular areas, suggesting localized interferon pathway activation but not a diagnostic pattern of cutaneous lupus erythematosus (Figure 3B). Direct immunofluorescence of lesional skin revealed scattered granular IgA and IgM deposits within cytoid bodies in the papillary dermis (Figure 3C-D). These nonspecific findings suggested inflammatory keratinocyte insult but, together with negative serology and the absence of typical histological changes, did not support lupus erythematosus [6].

Due to the persistent and progressive course, we performed repeated skin biopsies from flank, scalp, and back, which were reviewed by in-house dermatopathology and additionally discussed with reference pathology. These consistently demonstrated an acute to subacute spongiotic dermatitis with a dermal urticarial component. Immunohistochemistry demonstrated a predominantly CD3-positive T-cell infiltrate with a regular CD4/CD8 distribution of approximately 2:1 and sparse B cells with single CD30-positive cells. There was no cytological atypia, no aberrant loss of T-cell markers, and no histological evidence of cutaneous T-cell lymphoma. T-cell receptor clonality analysis of skin biopsy specimens demonstrated polyclonal TCRG and TCRB rearrangement patterns, without evidence of a clonal T-cell process. Periodic acid–Schiff staining did not reveal fungal elements, and there was no evidence of cutaneous CLL involvement or leukemia cutis.

Eosinophilic dermatosis of hematologic malignancy was considered, given the underlying CLL and the highly pruritic papulo-urticarial morphology. However, biopsies did not show an eosinophil-rich infiltrate [7]. Although individual eosinophils were present in one biopsy, the overall pattern was dominated by spongiotic/eczematous dermatitis, arguing against eosinophilic dermatosis of hematologic malignancy. The absence of a dense neutrophilic infiltrate also argued against Sweet syndrome. Drug-induced spongiotic dermatitis was considered. However, no relevant new systemic medication, including analgesics or over-the-counter medication, had been introduced before onset of the eruption. Contact dermatitis was considered less likely as use of new skin care products, detergents and other relevant exposures were denied. A primary atopic or other eczematous dermatitis remained a differential diagnosis, the absence of history of atopy and the atypical, treatment-refractory course favored consideration of a CLL-associated inflammatory process. Infection and infestation, including scabies, were not supported clinically.

During follow-up, the patient developed constitutional symptoms fulfilling the treatment criteria of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL). These included recurrent night sweats three times per week over two months, requiring bed linen changes without clinical evidence of infection. The patient suffered from fatigue associated with substantial limitations in usual daily activities, and unintentional weight loss of 9 kg (83 to 74 kg; 10.8%) within six months.

Absolute lymphocyte counts increased from 7.78 to 29.89 G/L within one month and remained elevated, suggesting rapid lymphocyte kinetics. Given that systemic corticosteroids may influence circulating lymphocyte counts, including through redistribution of CLL cells, the calculated lymphocyte doubling time was interpreted cautiously and considered in the overall assessment of disease activity [8]. Hemoglobin and platelet counts remained stable and above iwCLL thresholds excluding progressive bone marrow failure. Sonography revealed a normal-sized spleen and no bulky lymphadenopathy meeting iwCLL criteria. Several cervical, axillary, and inguinal lymph nodes were identified, without unequivocal evidence of progressive or symptomatic lymphadenopathy.

In the interdisciplinary hematologic assessment, treatment-requiring Binet stage A CLL was diagnosed based on iwCLL-relevant constitutional symptoms, in the context of increasing lymphocyte counts. The skin disease was not considered an independent iwCLL treatment indication, but subsequent improvement under CLL-directed therapy supports a paraneoplastic association. Leukocytosis alone was not considered an indication for treatment [1].

Obinutuzumab plus venetoclax was selected as a time-limited, chemotherapy-free targeted regimen supported by current CLL14 treatment data and considered appropriate for previously untreated CLL with favorable genetics (mutated IGHV, TP53 wild-type, no del(17p)), low tumor burden, and need for systemic therapy. Its fixed-duration schedule was advantageous in this prognostically favorable subgroup. Treatment followed the CLL14 schedule, with intravenous obinutuzumab during cycles 1–6 and oral venetoclax ramp-up from cycle 1 day 22 to 400 mg once daily, followed by fixed-duration venetoclax through cycle 12 [9,10].

Within one month after initiation of CLL-directed therapy, the cutaneous eruption regressed markedly (Figure 2G-I), with complete clearance of the scalp, only faint residual erythematous macules remaining, and substantial improvement of both pruritus and dermatology-related quality of life, as reflected by a decrease in the Dermatology Life Quality Index (DLQI) from 11 to 3. Absolute lymphocyte counts improved in parallel with the clinical skin response despite discontinuation of both systemic and topical corticosteroids (Figure 1). This close temporal relationship supports a paraneoplastic association between the spongiotic dermatitis and CLL activity, but does not prove causality.

Cutaneous manifestations in CLL include specific lesions, such as leukemia cutis, as well as nonspecific inflammatory or immune-mediated dermatoses and treatment-related skin adverse events. These may

pose a diagnostic challenge for dermatologists and hematologists alike [11]. Inflammatory dermatoses in patients with CLL are well recognized, particularly eosinophilic dermatosis of hematologic malignancy [7]. Paraneoplastic dermatoses may parallel malignancy activity, although their diagnostic and predictive value remains uncertain [12]. CLL-associated B- and T-cell dysregulation may contribute to inflammatory skin reactions, but the precise mechanisms underlying spongiotic dermatitis remain unclear [7].

The association between treatment-refractory dermatitis, progression to treatment-requiring CLL, and parallel improvement of skin lesions and absolute lymphocyte counts after CLL-directed therapy despite corticosteroid withdrawal supports a paraneoplastic relationship. Experimental CLL whole-blood assays demonstrate rapid B-cell-directed activity of obinutuzumab [13]. Because obinutuzumab preceded venetoclax, an independent anti-CD20-mediated effect on skin inflammation cannot be excluded, despite sparse B-cells in the cutaneous infiltrate, as circulating B-cell-dependent immune pathways may contribute. As cutaneous improvement occurred gradually, without a clearly identifiable onset, the individual contributions of obinutuzumab, venetoclax, and overall CLL control cannot be distinguished.

The novelty of this report lies in the onset of severe, therapy-refractory, generalized spongiotic dermatitis, documented by serial biopsies, which preceded the marked increase in lymphocyte counts and the subsequent recognition of treatment-requiring CLL by several months. This temporal sequence suggests that the skin eruption may have served as an early clinical warning sign of CLL progression, followed by improvement of both the cutaneous manifestations and hematologic disease under CLL-directed therapy. Previously reported CLL-associated eruptions include inflammatory-appearing lesions with leukemic infiltration [14] and eosinophilic dermatoses [15], whereas repeated biopsies in our patient consistently showed benign spongiotic dermatitis. Reference pathology and T-cell receptor clonality testing helped distinguish leukemia cutis, cutaneous T-cell lymphoma, Sweet syndrome, and eosinophilic dermatosis of hematologic malignancy; clinical history argued against drug-induced, contact, or infectious dermatitis. This case highlights the value of interdisciplinary clinical-pathological assessment in a paraneoplastic refractory skin disease as a potential early cutaneous indicator of CLL activity. Written informed consent for publication of the clinical details and images was obtained from the patient. This retrospective report was conducted in accordance with the ethical rules applicable in Germany and with the principles of the Declaration of Helsinki. According to local institutional requirements, formal review board approval was not required for this single-patient case report.

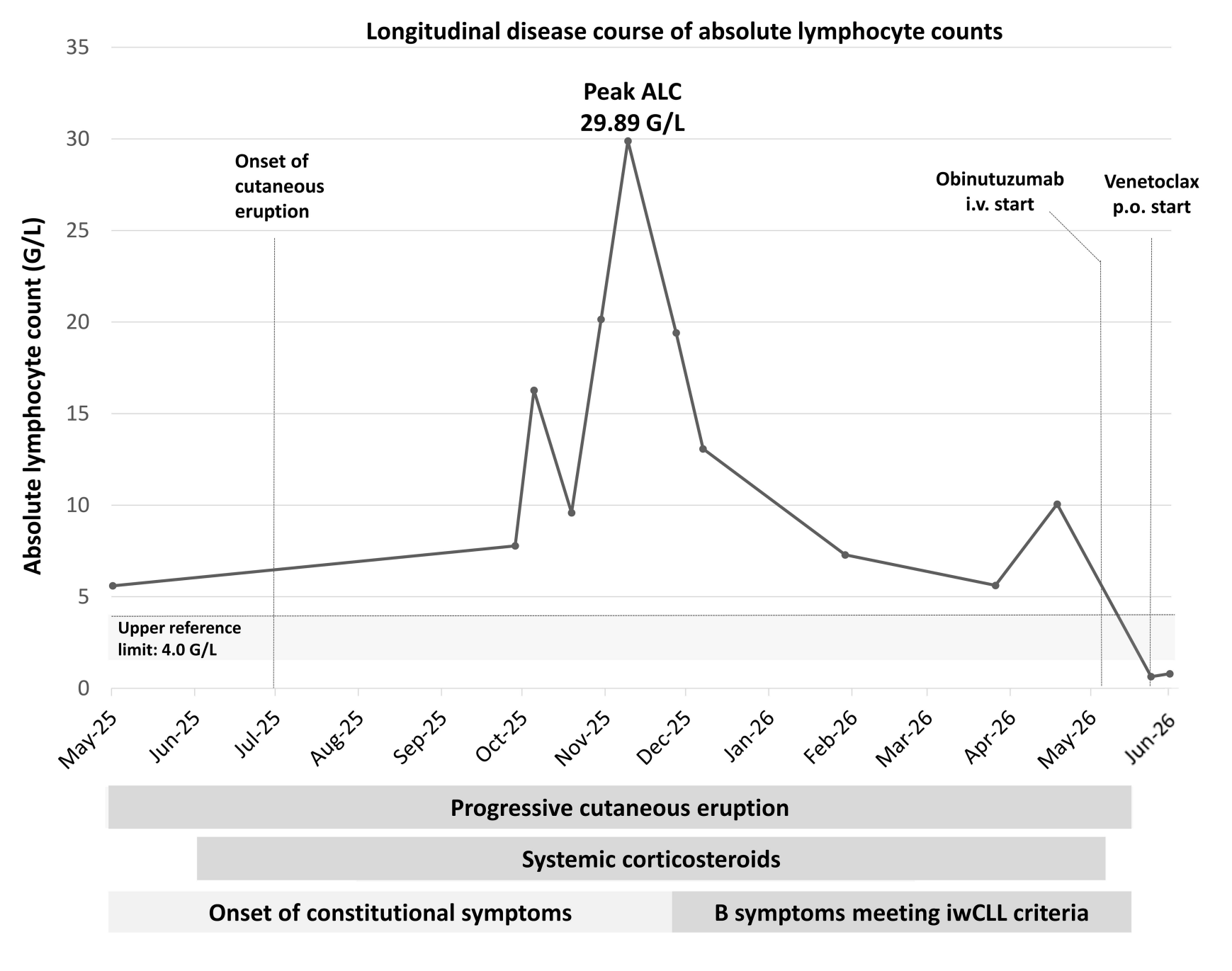
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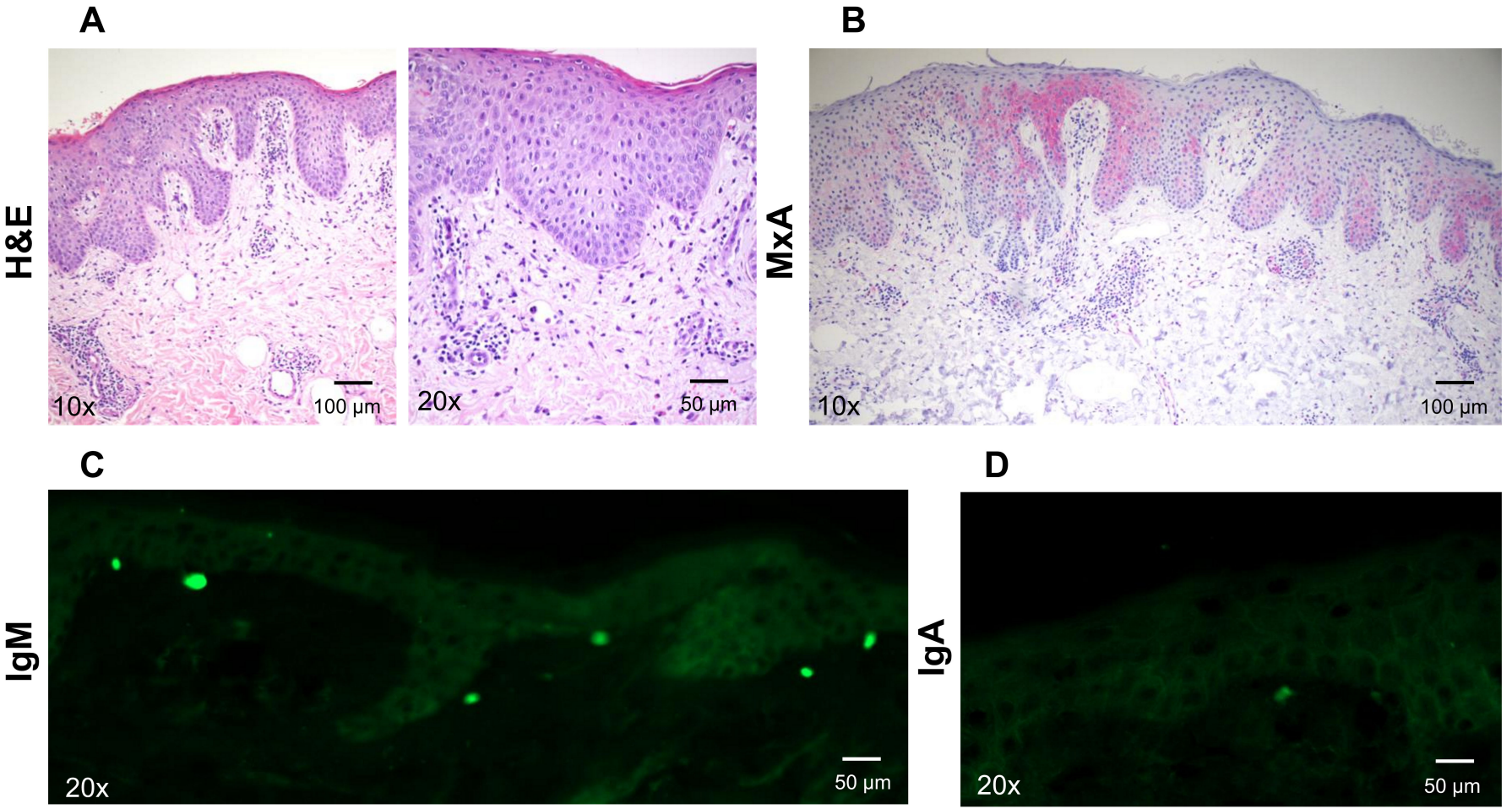
Figure 1. Longitudinal disease course of absolute lymphocyte counts, treatment exposure, and clinical response. Absolute lymphocyte counts (ALC) increased during the progressive, therapy-refractory inflammatory cutaneous eruption and peaked in November 2025. Total leukocyte counts were not used as the primary hematologic parameter because they may be confounded by systemic corticosteroid therapy, particularly through corticosteroid-induced neutrophilia. Systemic corticosteroids led to only temporary improvement and were tapered before initiation of CLL-directed therapy. CLL-directed therapy was initiated with intravenous (i.v.) obinutuzumab according to the CLL14 schedule during cycles 1–6, followed by oral (p.o.) venetoclax ramp-up starting on cycle 1 day 22 with escalation to the target dose of 400 mg once daily and fixed-duration continuation through cycle 12. After initiation of CLL-directed therapy, ALC declined in parallel with marked regression of the cutaneous eruption. The lower bars distinguish onset of constitutional symptoms from the period in which B-symptoms met iwCLL treatment criteria.

Figure 2. Clinical course of the cutaneous eruption over time. (A-C) Initial presentation in October 2025 before intensified dermatologic treatment, showing widespread erythematous macules and plaques on the trunk and extremities with partially confluent and annular configurations. **(D-F)** Follow-up in January 2026 during intensified topical therapy and phototherapy, with partial regression but persistent and undulating inflammatory skin lesions and pruritus. **(G-I)** Follow-up in June 2026, one month after initiation of CLL-directed therapy with obinutuzumab and venetoclax and after discontinuation of systemic and topical corticosteroids, showing marked clinical improvement with residual faint erythematous-telangiectatic macules and complete resolution of pruritus.

Figure 3. Histopathological and immunopathological findings. (A) Hematoxylin and eosin (H&E) staining demonstrates an acute to subacute spongiotic dermatitis with epidermal spongiosis, lymphocytic exocytosis, dermal edema, and a superficial perivascular lymphohistiocytic infiltrate with urticarial features. 10x, 20x magnification. (B) Myxovirus resistance protein A (MxA) immunohistochemistry shows focal expression in the epidermis. 10x magnification. (C) Direct immunofluorescence reveals scattered IgM- and (D) sporadic IgA-positive cytoid bodies in the papillary dermis. 20x magnification.


Longitudinal disease course of absolute lymphocyte counts
Absolute lymphocyte count (G/L)
35
30
25
20
15
10
5
0
Peak ALC
29.89 G/L
Onset of
cutaneous
eruption
Obinutuzumab
i.v. start
Venetoclax
p.o. start
Upper reference
limit: 4.0 G/L
May-25
Jun-25
Jul-25
Aug-25
Sep-25
Oct-25
Nov-25
Dec-25
Jan-26
Feb-26
Mar-26
Apr-26
May-26
Jun-26
Progressive cutaneous eruption
Systemic corticosteroids
Onset of constitutional symptoms
B symptoms meeting iwCLL criteria


A
D
G
B
E
H
C
F
I


A
H&E
10x
100 µm
20x
50 µm
B
MxA
10x
100 µm
C
IgM
20x
50 µm
D
IgA
20x
50 µm