SHORT COMMUNICATION

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The Absence of Recent Systemic Therapy can be a Significant Risk Factor for Nemolizumab-associated Cutaneous Adverse Events in Patients with Prurigo Nodularis: A Single-centre Retrospective Study

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Prurigo nodularis (PN) is characterized by intensely pruritic papules and nodules. Similar to atopic dermatitis (AD), PN development is driven by the "itch–scratch cycle", with T helper (Th)2-dominant chronic inflammation and neural pathways playing key roles in the pathogenesis (1, 2). In addition to conventional PN treatments, targeted biologic therapies have recently emerged as promising options. Dupilumab, an interleukin (IL)-4/IL-13 inhibitor, and nemolizumab, an IL-31 receptor antagonist, have both demonstrated significant improvements in pruritus and skin lesions, leading to their approval for PN (3–5). Cutaneous adverse events (cAEs) such as oedematous erythema have been reported in 10–40% of nemolizumab-treated patients (6). However, the underlying mechanisms remain unclear, and no standardized management strategies have been established. These cAEs can be severe and generalized, leading to treatment discontinuation. Given their clinical impact, identifying cAE risk factors is essential. Few studies have explored this, so we conducted a single-centre analysis to investigate the potential risk factors of nemolizumab-related cAEs.

MATERIALS AND METHODS

Study design and patients

This retrospective study was conducted in the Department of Dermatology, Tokyo Metropolitan Police Hospital, between April 2024 and April 2025. Overall, 22 men and 13 women with PN who received nemolizumab (initial 60 mg dose followed by 30 mg monthly) and underwent follow-up for at least 12 weeks after the initial dose were included. All other systemic therapies were discontinued during nemolizumab treatment. Diagnosis and treatment were based on the 2024 Japanese Dermatological Association Guidelines for PN, primarily targeting patients with a PN-Investigator's Global Assessment (PN-IGA) score of 3 or 4 and a Peak Pruritus Numerical Rating Scale (PP-NRS) score of ≥ 7. One patient with a PP-NRS score of <7 after dupilumab treatment but who maintained a PN-IGA score of 3 was also included. The cohort included patients with underlying AD who developed multiple PN lesions owing to chronic scratching. The analysis also included 7 previous cases from our institution (7–10). The following baseline data were collected: age, sex, body mass index (BMI), treatment history, comorbidities, laboratory test values (eosinophil count, lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC), and IgE), and PP-NRS and PN-IGA scores. Only systemic or topical therapies continuously administered for at least 1 month were considered part of the treatment history; short-term (<1 month) rescue treatments were excluded. BMI, eosinophil count, LDH, TARC, and IgE data were missing in 15, 10, 13, 16, and 17 cases, respectively.

At each monthly visit, patients were carefully interviewed regarding any new skin symptoms following nemolizumab administration, and a full-body skin observation was performed to assess cAEs. As most cAEs are reported within the first 3 doses, the observation period was set at 12 weeks (11). Patients were categorized into cAE and non-cAE groups, and background factors, including age, sex, BMI, previous treatments, comorbidities, and various laboratory parameters, were compared to identify potential risk factors for cAE development.

This study was approved by the ethics committee of Tokyo Metropolitan Police Hospital (approval no. 25-A03) and conducted as per the Declaration of Helsinki (2004 revision).

Statistical analysis

For intergroup comparisons, continuous variables with non-parametric distributions (e.g., age and laboratory data) were analysed using the Mann–Whitney *U* test. Categorical variables (e.g., comorbidities, treatment history) were analysed using Fisher's exact test. A p-value of <0.05 was considered significant. All analyses were performed using EZR (Easy R; https://www.jichi.ac.jp/usr/hema/EZR/statmedEN.html) software.

RESULTS

The mean age of patients was 76 years. Most (97.1%) had received oral antihistamines and topical corticosteroids. Prior treatments included dupilumab (17.1%), phototherapy (11.4%), and other systemic therapies such as lebrikizumab (2.9%). Comorbidities included cardiovascular disease (25.7%), hypertension (48.6%), and diabetes (28.6%), reflecting frequent metabolic and cardiorenal conditions. Baseline PP-NRS and PN-IGA scores averaged 8.28 and 3.09, with mean eosinophils 304/μL, LDH 182 IU/L, TARC 378 pg/mL, and IgE 172 IU/ml (**Table I**). All 11 patients with prior systemic therapy continued this until immediately before nemolizumab initiation, with a median duration of 11.5 weeks for dupilumab and 18 weeks overall (**Table II**). During the 12-week observation period, 10 patients (28.6%) developed cAEs, including *Malassezia* folliculitis ($n=2$), purpura ($n=1$), psoriasis-like eruption ($n=1$), erythema ($n=3$), acute eczema ($n=2$), and urticaria ($n=1$). Regarding the onset time, cAEs occurred after the first, second, and third doses in 6, 2, and 2 cases, respectively.

We compared patients with cAEs within 12 weeks ($n=10$) with those without ($n=25$). Recent systemic therapy was more common in the non-cAE group (0% vs 44%, $p=0.0146$), indicating that lack of recent systemic treatment may increase cAE risk. Indeed, no cAEs

Table I. Baseline characteristics of patients with prurigo nodularis in this study and comparison of background factors between patients with and without cutaneous adverse events due to nemolizumab ($n = 35$)

Background factors or baseline values of indexes	All patients ($n = 35$)	Patients with cAEs ($n = 10$)	Patients without cAEs ($n = 25$)	p-value
Age, median [IQR]	76 [61–82]	77 [65–82]	66.5 [54.5–80]	0.297
Male sex, *n* (%)	22 (63%)	6 (6%)	16 (64%)	1
Body mass index, kg/m², median [IQR]	22.2 [20.7–24]	21.8 [20.1–23.1]	23.5 [22.3–24.7]	0.248
PP-NRS score, median [IQR]	8 [7–9]	8 [7–9]	9 [8.25–9.75]	0.189
PN-IGA score, median [IQR]	3 [3–3]	3 [3–3]	3 [3–3]	0.275
Eosinophil count/μL, median [IQR]	304 [200–600]	318 [200–586]	300 [200–600]	0.973
LDH, IU/L, median [IQR]	182 [165–239]	189 [167–242]	167 [159–178]	0.268
TARC, pg/mL, median [IQR]	378 [264–887]	341 [222–1044]	601 [354–845]	0.736
IgE, IU/mL, median [IQR]	172 [39–1163]	115 [33.7–518]	699 [45.6–1353]	0.703
Comorbidities, *n* (%)				
Atopic dermatitis	9 (26%)	4 (40%)	5 (20%)	0.393
Cardiovascular disease	9 (26%)	1 (10%)	8 (32%)	0.235
Hypertension	17 (49%)	4 (40%)	13 (52%)	0.711
Diabetes mellitus	10 (29%)	2 (20%)	8 (32%)	0.686
Hyperlipidaemia	8 (23%)	1 (10%)	7 (28%)	0.393
Renal dysfunction	5 (14%)	1 (10%)	4 (16%)	1
Malignancies	2 (5.7%)	2 (20%)	0 (0%)	0.0756
Mental disorder	3 (8.6%)	2 (20%)	1 (4.0%)	0.19
Previous treatment, *n* (%)				
Phototherapy	4 (11.4%)	1 (10%)	3 (12%)	1
Dupilumab	6 (17.1%)	0 (0%)	6 (24%)	0.152
Biologics	7 (28%)	0 (0%)	7 (28%)	0.0835
Systemic therapy	11 (44%)	0 (0%)	11 (44%)	0.0146*

IQR: interquartile range; cAEs: cutaneous adverse events; PP-NRS: peak pruritus numerical rating scale; PN-IGA: prurigo nodularis Investigator's Global Assessment; LDH: lactate dehydrogenase; TARC: thymus and activation-regulated chemokine; IgE: immunoglobulin E. *$p < 0.05$ was considered statistically significant.

occurred in patients with recent systemic therapy, while 41.6% (10/24) without such treatment history developed cAEs. No other comorbidities or prior treatments were significantly associated with cAEs.

DISCUSSION

A recent Japanese retrospective study of 219 cases found no significant associations between cAE occurrence and baseline characteristics or laboratory parameters (11), while we newly demonstrated that a history of systemic therapy was associated with a lower incidence of cAEs. The exact mechanisms underlying nemolizumab-associated cAEs remain unclear; however, activation of Th2-driven inflammation following IL-31 inhibition has been proposed as a contributing factor (12–14). In IL-31 knockout mice, oncostatin M-dependent IL-4 and IL-13 upregulation has been observed, supporting the hypothesis of enhanced Th2 inflammation (12, 13). Furthermore, transient TARC elevation was observed in about 5% of patients, associated with the development of oedematous erythema and acute eczema (14,15). Our previous report of TARC and eosinophil increases during cAEs, which declined with clinical improvement, support this hypothesis (7).

Table II. Duration of systemic therapies in patients with prurigo nodularis prior to nemolizumab initiation

Patient	Systemic treatment	Treatment duration
1	Dupilumab	4 weeks
2	Dupilumab	9 weeks
3	Dupilumab	11 weeks
4	Dupilumab	12 weeks
5	Dupilumab	13 weeks
6	Dupilumab	18 weeks
7	Cyclosporin	24 weeks
8	Cyclosporin	104 weeks
9	Oral corticosteroid	156 weeks
10	Difelikefalin	26 weeks
11	Lebrikizumab	20 weeks

In this study, we hypothesized that patients with a recent systemic immunomodulatory therapy, such as dupilumab, lebrikizumab, corticosteroids, or cyclosporine, may have achieved sufficient Th2 inflammation suppression before nemolizumab administration. Baseline characteristics were not associated with cAEs, whereas patients who developed cAEs tended to show transient TARC increase (11, 14). These findings suggest that the recent systemic immunomodulation may mitigate the risk of Th2 rebound activation, thereby reducing the likelihood of cAE occurrence. However, it is important to note that we did not perform longitudinal assessments of blood markers before and after treatment, so this hypothesis remains speculative. Beyond oedematous erythema, acute eczema, and urticaria, other cAEs may involve distinct immune pathways (6). Psoriasiform eruptions and *Malassezia* folliculitis may be triggered by secondary Th17 activation following IL-31 blockade. Purpura may involve not only T-cell activation but also B-cell activation. However, the precise mechanisms remain unclear (6).

To our knowledge, this may be the first retrospective study to investigate potential risk factors for nemolizumab-induced cAEs in patients with PN, suggesting that the lack of recent systemic therapy is a significant risk factor for cAEs. However, although risk factors have been identified, it remains entirely unclear which patients experience TARC elevation and Th2 activation following

nemolizumab treatment. Additionally, this study has several limitations. It was a single-centre retrospective study with a small sample size and a short observation period; BMI and blood test parameter data were missing; and treatment-related changes in blood markers were not evaluated over time. Future studies with larger cohorts and longitudinal data are needed to identify patients in whom TARC elevation and Th2 activation occur after nemolizumab, clarifying cAE risk factors and its fundamental mechanisms.

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Data availability: Data concerning this article may be requested from the corresponding author for reasonable reasons.

IRB approval status: This study was approved by the Ethics Committee of the Tokyo Metropolitan Police Hospital (approval no. 25-A03) and was conducted in accordance with the Declaration of Helsinki (2004). Informed consent was obtained from all participants through an opt-out process.

Conflict of interest disclosures: YM and KI have received lecture fees from Maruho Co., which markets nemolizumab.

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