

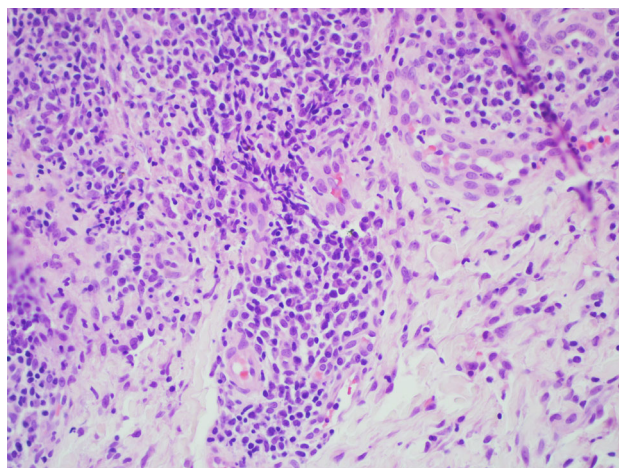


Figure 2 Histopathology shows dermal perivascular infiltrate of lymphocytes, plasma cells, histiocytic, multinucleated cells, focal necrosis and initial granulomas (original magnification 200×).

and primarily the rich plasma cell infiltrate were consistent with benign tertiary syphilis.

Serology resulted positive for both treponemal and non-treponemal tests: Treponema pallidum hemagglutination assay (TPHA) titre was 1:10240 and venereal disease research laboratory (VDRL) titre was 1 : 64; anti-*T.pallidum* IgM antibodies were also positive. Neurological, ophthalmological and cardiological examination, brain magnetic resonance imaging and echocardiogram were normal. However, cerebrospinal fluid (CSF) testing revealed mononuclear pleocytosis (cell count 9 μ L), reactive TPHA with titre of 1 : 1280, intrathecal CSF IgG-Index of 0.9 and TPHA index of 136. Anti-*T.pallidum* IgM antibodies in CSF resulted negative.

The patient was ultimately diagnosed with asymptomatic neurosyphilis and therefore treated with aqueous penicillin G, four million units intravenously every 4 h for 14 days. The cutaneous lesions resolved with scarring in 4 weeks (Fig. 1c,d); after 6 months, in the serum, VDRL and TPHA titres declined six-fold and anti-*T.pallidum* IgM antibodies resulted weakly positive.

This case was interesting not only for the deceiving patient's history but especially for the clinical aspect of the cutaneous lesions, given the rarity, nowadays, of benign tertiary syphilis (*gummas*) in clinical practice. Syphilitic nodules may mimic lymphoproliferative disorders, granulomatous disorders, deep fungal and mycobacterial infections.^{1,2,5,6} Close collaboration with the pathologist and finding a rich plasma cell infiltrate helped solve this case. Notably, even in absence of any neurological signs or symptoms, our patient had a neurologic involvement confirmed by CSF abnormalities. CSF testing is crucial for the correct diagnosis and therapeutic approach, also in case of asymptomatic neurosyphilis.⁶ Even if the patient's history is not

evocative for STDs, as in our case, syphilis should be considered when approaching granulomatous lesions of unclear nature.

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Conflict of interest

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Response to dupilumab in two children with Netherton syndrome: Improvement of pruritus and scaling

Dear editor

Netherton syndrome (NTS) (MIM#256500) is an ichthyosis caused by *SPINK5* mutations. The gene encodes the serine

protease inhibitor LEKTI. Patients show erythema, scaling, severe pruritus, atopic manifestations, growth retardation and an increased susceptibility towards infections, making treatment of NTS challenging.¹ Because of its clinical and pathophysiologic overlap with atopic dermatitis (AD) due to dysregulated protease activities², dupilumab (interleukin (IL)-4/IL-13 antagonist) could be effective. We report on two children with NTS treated with dupilumab. Disease severity was determined by the Nether-ton Area Severity Assessment (NASA; 0-72) and the Physician Global Assessment (PGA; 0-5).^{3,4} Pruritus intensity was evaluated by a numeric rating scale (NRS; 0-10; recall period: average intensity, 24 h).

A 12-year-old female patient was treated for twelve months, initially with 600 mg dupilumab followed by 300 mg every four weeks. The therapy was intensified (200 mg biweekly) after four months (age and weight adapted approved dosage in Germany for AD). She did not have concomitant systemic therapy, except for growth hormone and vitamin D. NASA decreased from 33 to 11.7 after 4 months of treatment. PGA showed a similar course (Table 1). Erythema almost disappeared; scaling was less pronounced. Dupilumab was well tolerated. Pruritus initially dropped by 4 NRS points to a moderate degree. After

10 months, she showed bacterial superinfection. Even though the NASA increased, pruritus remained moderate. After treatment of bacterial superinfection with topical antiseptics, severity of dermatitis improved again (Table 1).

The second patient (8-year-old, male) received dupilumab 300 mg every 4 weeks for ten months (dosage according to clinical trial for AD (Prot#R668-AD-1434)). He had been treated with subcutaneous immunoglobulins (IGs) for 5 years. This therapy was clinically more or less beneficial; he still suffered from extreme pruritus. Before adding dupilumab to IGs, NASA and PGA were high. These parameters then decreased by at least 50% within 10 months (Fig. 1). On NRS, pruritus rapidly improved (Table 1). Dupilumab and its dosage were well tolerated. Considering the positive response, we reduced IGs (from weekly to biweekly) after 10 months.

In an attempt to capture inflammatory activity in case 1, levels of IL-1 β , IL-17A, IL-1 receptor antagonist (IL-1RA), IL-6, MIG/CXCL9 and IL-18 were quantified by a multiplexed bead array assay as described previously.⁵ Eosinophil counts were determined in both cases. For case 1, the systemic levels of IL-1 β , IL-6 or IL-17A at baseline and on month 10 did not show differences, but we observed a slight increase in the

Table 1 Clinical scores, interleukin serum profile and eosinophil count before and after beginning of treatment with dupilumab

Patient	Observation time (in months)	NASA (0-72) [erythema (E); infiltration (I); lichenification (L); scaling (S) (0-3)]	PGA (0-5)	NRS (pruritus, 0-10)	IL-1 β (pg/mL)	IL-6 (pg/mL)	IL-17A (pg/mL)	IL-1RA (pg/mL)	CXCL9 (pg/mL)	IL-18 (pg/mL)	Eosinophil count (in % and Tsd/ μ L)
Case 1	0*	33 [E: 1; I: 1; L: 2; S: 2]	4	8	1.48	0.33	0.3	111.13	25.37	7.79	4.2 0.37
	2	24.4 [E: 1; I: 1; L: 1; S: 1]	3	4	-	-	-	-	-	-	-
	4	11.7 [E: 0; I: 1; L: 1; S: 1]	2	3	-	-	-	-	-	-	-
	10	31.6 [E: 2.5; I: 1; L: 1.5; S: 1]	4	3	1.39	0.33	0.31	160.26	19.02	9.05	1.2 0.13
	12	11.7 [E: 1; I: 1; L: 1; S: 1.5]	2	2	-	-	-	-	-	-	-
Case 2	0*	50.5 [E: 2; I: 1.5; L: 2; S: 2.5]	4	8	-	-	-	-	-	-	1.9 0.15
	4	46.3 [E: 1; I: 1; L: 2; S: 2]	3	4	-	-	-	-	-	-	-
	10	18.0 [E: 1; I: 1; L: 1; S: 1]	2	3	-	-	-	-	-	-	-
Healthy controls (n = 8)	10	-	-	-	4.5 [3.9-7.6]	2.7 [2.0-14.2]	0.6 [0.5-2.0]	898.3 [27.3-2850.6]	21.4 [5.6-179.1]	6.4 [4.4-27.4]	-

Marked improvement of pruritus, NASA and PGA in both cases. Median levels of IL-1 β , IL-6 and IL-1RA were decreased in case 1 in comparison with eight age- and sex-matched healthy controls. IL-1RA showed a slight increase under therapy with dupilumab. Data of healthy controls are shown as median [range].

The NASA score relates to the Eczema Area and Severity Index (EASI) and assesses severity of dermatitis (E = erythema, I = infiltration/papulation, L = lichenification, S = scaling) over four body areas. Scoring signs are separately listed, ranging from none (0) to severe (3). Reference values for eosinophil count: 0-3.4%; 0.02-0.32 Tsd/ μ L. General blood and serum parameters have been checked regularly and were normal.

*Before treatment with dupilumab.

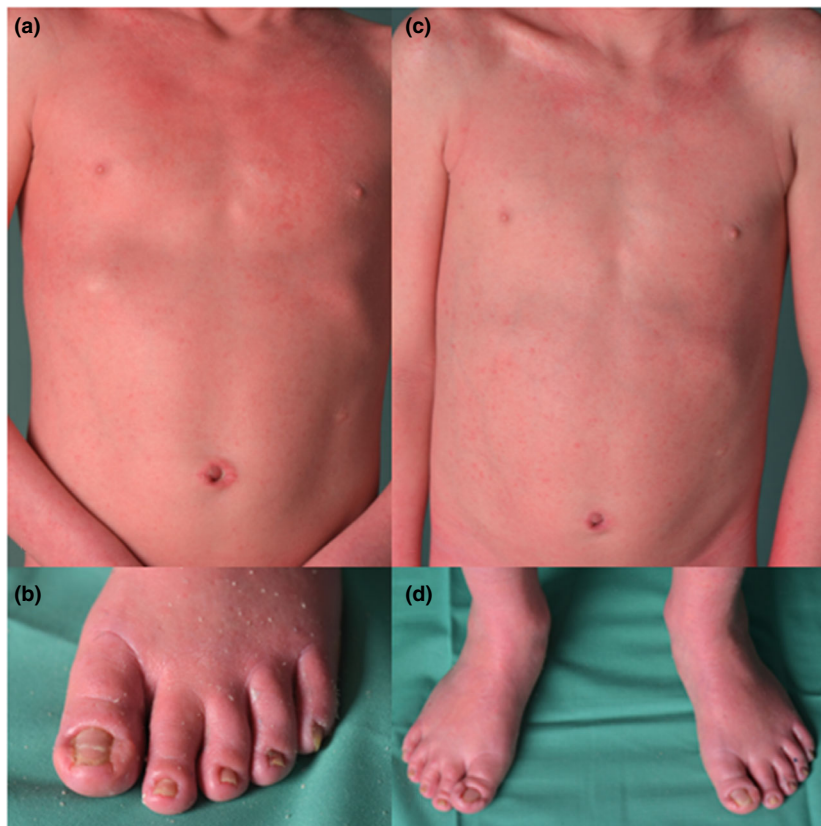


Figure 1 Case 2 (8-year-old, male) with NTS treated with dupilumab and immunoglobulins. Patient before treatment with dupilumab (immunoglobulins only) (a,b) and 10 months after the first application of dupilumab (c,d). Erythema (a) and scaling (b) are less pronounced after ten months (c,d).

IL-1RA concentration and a feeble reduction for CXCL9. Compared to healthy controls, our patient tends to have lower levels of IL-1RA, IL-1 β and IL-6. Her eosinophil count dropped. IgE levels changed from >5000 kU/l to 1980 IU/mL (case 2: from 1628 to 516 IU/mL). Interestingly, eosinophils in case 2 were already normal before adding dupilumab (Table 1).

These clinical observations suggest that children with NTS may highly benefit from dupilumab. The response of NTS to dupilumab has been published for one adult patient so far.⁶ Similarly, we observed a strong improvement of pruritus and scaling, partially on erythema. Dupilumab was well tolerated also in the combination with IGs. Concerning dupilumab dosing in young children with NTS, we think a dosage of 300 mg every 4 weeks is well tolerated in children older than 6 years. Bacterial superinfections explained the transient worsening of erythema in case 1. Of note, she reported a reduced overall frequency of cutaneous infections (from >4×/year to 3×/year). The quantification of systemic cytokine/chemokine levels did reveal only slight differences before and during therapy and compared to healthy controls. Since we only quantified systemic cytokines/chemokines, we cannot exclude an alteration of the local skin profile as published previously.^{1,7} We report on a limited number of patients. To obtain a full picture and respond to questions

concerning dosage, tolerance and long-term safety, clinical trials, and further research on immunological parameters of NTS are required.

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Access to Data and Data Analysis

Dr. Kira Süßmuth (as the corresponding author) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

Potential conflicts of interest involving the work under consideration for publication (during the time involving the work, from initial conception and planning to present): Prof. Sonja Ständer received fees for advisory board and lectures for Sanofi and is an investigator for Sanofi. The other authors (Dr. Kira Süßmuth, Prof. Heiko Traupe, Prof. Karin Loser, Dr. Christoph Kessel, Dr. Helmut Wittkowski, Dr. Vinzenz Oji) do not have any potential

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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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Carrying out local care for epidermal necrolysis: survey of practices

Dear Editor

Patients with epidermal necrolysis (EN, Stevens–Johnson syndrome and toxic epidermal necrolysis) are managed in dermatology, intensive care units (ICU) or burn centres. Guidelines emphasize the key role of supportive care, especially for the prevention of infections.^{1–3} However, data reporting on practical modalities of skin and mucosal care remain scarce. We aimed to conduct an audit of practices for local care of patients with EN in France.

We conducted a survey of practices in institution partners of the French National Reference Centre for EN. A standardized questionnaire recorded the profile of department, room, the target ambient temperature, water filtration, caregivers' personal protective equipment used for patient nursing, dressings and logistical aspects of wound care/nursing (*i.e.* number of caregivers involved, duration and periodicity, skin antisepsis, skin debridement).

Data were collected from 13 departments (dermatology, *n* = 6; ICU, *n* = 2; burn centres, *n* = 5; details on the recruitment of each department during the 2018–2019 period is provided in the Fig. 1). Patient rooms were single in all cases (sterile flow rooms in 4 burn centres). Room temperature was kept