

## INVESTIGATIVE REPORT

# IL-31 Does not Correlate to Pruritus Related to Early Stage Cutaneous T-cell Lymphomas but is Involved in Pathogenesis of the Disease

Marta MALEK<sup>1,2</sup>, Jolanta GLEŃ<sup>1</sup>, Krzysztof REBAŁA<sup>3</sup>, Anna KOWALCZYK<sup>2,4</sup>, Michał SOBJANEK<sup>1</sup>, Roman NOWICKI<sup>1</sup>, Katarzyna RUCKEMANN-DZIURDZIŃSKA<sup>5</sup> and Małgorzata SOKOŁOWSKA-WOJDYŁO<sup>1,2</sup>

<sup>1</sup>Clinic of Dermatology, Venereology and Allergology, <sup>2</sup>Department of Forensic Medicine, <sup>4</sup>Clinic of Oncology & Radiotherapy, <sup>5</sup>Department of Pathology and Experimental Rheumatology, Medical University of Gdańsk, and <sup>3</sup>Polish Lymphoma Research Group, Poland

**Mycosis fungoides (MF) and Sézary syndrome (SS) belong to the group of primary cutaneous T-cell lymphomas (CTCL). Regardless of the stage of the disease, patients with MF and SS can suffer from chronic pruritus. The aim of the study was to investigate the correlation between the interleukin 31 (IL-31) serum level, the degree of pruritus and CTCL severity; and to compare the frequency of IL-31 gene polymorphisms between patients and the control group, and between patients at different stages of the disease. Pruritus affected 67.7% of patients with MF and SS in our study. The IL-31 serum level was significantly higher in CTCL patients than in the control group but there were no positive correlation between IL-31 serum level and pruritus. A statistically significant difference in allele frequencies for IL-31 IVS2+12 gene polymorphisms between early and advanced stages was detected; GAG haplotype was more frequent and AGA was less frequent in stage IA patients compared with patients in the other stages of the disease. Key words: mycosis fungoides; Sézary syndrome; interleukin 31; polymorphism; cutaneous T-cell lymphoma.**

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Dr Marta Malek, Clinic of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Dębinki 7, PL-80-211, Gdańsk, Poland. E-mail: m.malek@gumed.edu.pl

Mycosis fungoides (MF) and Sézary syndrome (SS) belong to the group of primary cutaneous T-cell lymphomas (CTCL) (1, 2). MF is characterised by patches and plaques, which may progress to nodules, tumours, lymph nodes and blood involvement. SS is the leukaemic variant of CTCL marked by erythroderma, enlarged lymph nodes and abnormal lymphocytes in the peripheral blood (3–6). The incidence rate per 100,000 person-years is 0.55 for MF and 0.01 for SS. The diseases are more common in men (M:F ratio = 1.57) and in black patients (black/white ratio = 1.55) (7).

Regardless of the stage of the disease, patients with MF and SS can be affected by chronic, severe pruritus, which can be very debilitating and adversely influence patients' quality of life (8, 9). Depending on the studied group this symptom affects 60–100% of patients with CTCL (8–14).

In patients with CTCL, pruritus is permanent, and is aggravated in the evening by heat and by water. Most patients report diffuse pruritus, but it can also be limited to skin lesions. Pruritus can be the earliest symptom of CTCL and may occur without skin lesions. It is particularly severe in patients with SS, and folliculotropic and erythrodermic types of MF (15, 16).

The pathomechanism of pruritus in patients with CTCL is not fully understood. Antihistamines, routinely used with success in pruritic dermatoses, are not as effective in patients with CTCL. Therefore it seems that, besides histamine, other mediators play a role in the pathogenesis of this symptom. According to the literature these mediators include: opioids, gastrin-releasing peptide, substance P, serotonin, proteinases and interleukins (15, 16).

Interleukin 31 (IL-31), discovered in 2004 (17), is secreted mainly by activated Th2 cells. Mast cells are also a source of this cytokine (17–19). Moreover, in response to ultraviolet irradiation (UV) and hydrogen peroxide monocytes, macrophages, immature and mature monocyte-derived dendritic cells produce IL-31 (20). IL-31 is related to the IL-6 cytokine family by its structure and receptor complex (21). IL-31 signals through a heteromeric receptor complex composed of the IL-31 receptor alpha (IL-31 RA) and the oncostatin M receptor beta (OSMR) subunits. The receptor is mainly found on keratinocytes and monocytes. Binding of the receptor complex first activates Janus kinase (JAK) and then activates signal transducers and activators of transcription (STAT), mitogen-activated protein-kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways (22–24).

The involvement of this interleukin in the pathogenesis of pruritus is supported by many reports in the literature. Significantly higher levels of IL-31 were found in the skin biopsies taken from patients suffering from pruritic skin diseases compared to those without itching (25). Higher serum IL-31 levels were also confirmed in pruritic cases of CTCL when compared to non-pruritic ones (26).

## MATERIALS AND METHODS

### Participants

The study group included 62 patients (43 males, 19 females, mean age 60.7 ± 15.3 years, age range 20–86 years) with CTCL (60 MF cases, 2 SS cases) treated at the Department of Dermatology, Ve-

neurology and Allergology of the Medical University of Gdansk between 2012 and 2013. Patients were staged: IA (21 cases), IB (24 cases), IIB (8 cases), III (4 cases) and IV (5 cases) according to the staging system proposed by the International Society of Cutaneous Lymphoma (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) (1, 2). Patients at stage IA-IB were defined as early stages, IIB-IV as advanced stages. 96 healthy controls (mean age  $27.46 \pm 7.88$  years, range 18–52) with no history of allergy, atopic dermatitis (AD), CTCL or other immune diseases were enrolled in the study.

This study was approved by the medical ethics committee of the Medical University of Gdansk and was conducted according to the principles of the Declaration of Helsinki.

### Pruritus

The assessment of pruritus severity was performed with Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS) (VAS, NRS:  $> 0-3$  = mild;  $> 3-7$  = moderate;  $> 7-9$  = severe;  $> 9$  very severe).

### Protein assay using ELISA and amplification refractory mutation system-PCR

Genomic DNA was prepared from the whole blood samples using Blood DNA Prep Plus (A&A Biotechnology, Gdansk, Poland) following the instructions of the manufacturer. Analysis of polymorphic variants of IL-31 gene was performed by an amplification refractory mutation system PCR (ARMS PCR) method using self-designed specific sequences of oligonucleotides, with internal amplification control of growth hormone 1 (GH1) fragment: GH1-F GCCTTCCCAACCATCCCTTA and GH1-R TCACGGATTTCTGTTGTGTTTC. PCR conditions were as follows: 5 min at  $94^{\circ}\text{C}$  (initial denaturation); 34 cycles of 40 s at  $94^{\circ}\text{C}$ , annealing step for 60 s at  $64^{\circ}\text{C}$  for IL-31-2057,  $62^{\circ}\text{C}$  for IL-31-1066,  $53^{\circ}\text{C}$  for IL-31 IVS2+12 and 90 s at  $72^{\circ}\text{C}$ ; and finally  $72^{\circ}\text{C}$  for 5 min. The PCR products were separated on 2% agarose gels and stained with ethidium bromide.

IL-31 protein levels were measured using standard ELISA kits (Bender MedSystems GmbH, Vienna, Austria). All analyses were performed according to the manufacturer's protocol.

### Statistical analysis

The results were evaluated by Fisher's exact test, Mann-Whitney *U* test and Spearman's rank correlation test with the use of STATISTICA 10 software (StatSoft). IL-31 haplotype frequencies were estimated by means of tagging SNPs identified in the German population by Schulz et al. (27), a maximum-likelihood approach, implemented in an expectation-maximization (EM) algorithm, and a Bayesian approach with a Gibbs sampling strategy, implemented in the Excoffier-Laval-Balding (ELB) algorithm. Computations were performed with Arlequin 3.1 software (28). A *p*-value of  $< 0.05$  was considered statistically significant.

## RESULTS

### Medical history

The mean age of the 60 patients with MF and 2 patients with SS at debut of their skin lesions was 54.3 and 48.5 years, respectively. The mean age at which CTCL was first diagnosed was 59.3 in patients with MF and 53.3 with SS. A diagnosis was made before the age of 20 in only one case. Diseases of the cardiovascular system (26 cases) and diabetes (10 cases) were the most common

co-morbidities. Other malignancies, current or in the past, were noted in 4 patients.

### Pruritus

The prevalence of pruritus in all patients was 67.7%. The mean pruritus severity score for all patients was 2.9 (VAS) and 2.8 (NRS). The mean pruritus scores in patients with early and advanced stage disease were 2.6 (VAS), 2.4 (NRS) and 3.8 (VAS), 4.0 (NRS). There was a statistically significant difference in NRS between the early and the advanced stages ( $p=0.036$ ). The mean pruritus scores in patients with stages IA and IV were 1.9 (VAS), 2.0 (NRS) and 4.6 (VAS), 4.7 (NRS), respectively. This difference was statistically significant (VAS  $p=0.045$ ; NRS  $p=0.049$ ). The highest mean pruritus scores were found in patients with erythroderma (IIIMF+SS): (VAS 5.2), (NRS 5.2), but it was not statistically significant compared to other patients (IA+IB+IIB+IVMF).

### IL-31

The median and mean  $\pm$  SD serum IL-31 levels in healthy controls were 0.000 pg/ml (IQR 0.000) and  $0.208 \pm 0.709$  pg/ml (range: 0–4.1 pg/ml), compared to 3.681 pg/ml (IQR 0.524) and  $3.802 \pm 0.783$  (range: 2.717–7.553 pg/ml) in the patients ( $p=0.00001$ ). Serum IL-31 levels were still significantly higher for each subgroup compared to those of the normal controls (I, IIB, IV  $p=0.00001$ ; III  $p=0.001$ ) (Fig. 1, Table SI<sup>1</sup>).

### Serum IL-31 in relation to pruritus

No positive correlation was found between serum IL-31 levels and severity of pruritus in the whole group of CTCL patients ( $p=0.894$ ,  $R=0.017$ ) (Fig. 2). The intensity of pruritus correlated with serum IL-31 concentrations only in stage IB ( $p=0.024$ ,  $R=0.458$ ). There were no statistically significant differences in serum IL-31 levels between pruritic cases of CTCL (median 3.687 pg/ml, IQR 0.582; mean  $3.714 \pm 0.495$ ) and non-pruritic ones (median 3.680 pg/ml, IQR 0.462; mean  $3.680 \pm 0.462$ ) ( $p=0.640$ ).

### The genetic variant polymorphisms

Distribution of the genotypes for IL-31 polymorphisms was consistent with a Hardy-Weinberg equilibrium in CTCL and control group. There were no statistical differences in the frequencies of alleles, genotypes and haplotypes between CTCL patients and control group.

The frequency of the allele G for the IL-31 IVS2+12 gene polymorphisms was higher in the early (38.9%) than in advanced stages (20.6%) ( $p=0.041$ ). The frequency of haplotype GAG was higher in patients with stage IA (EM-14.3%, ELB-9.5%; see *Statistical analysis*) than

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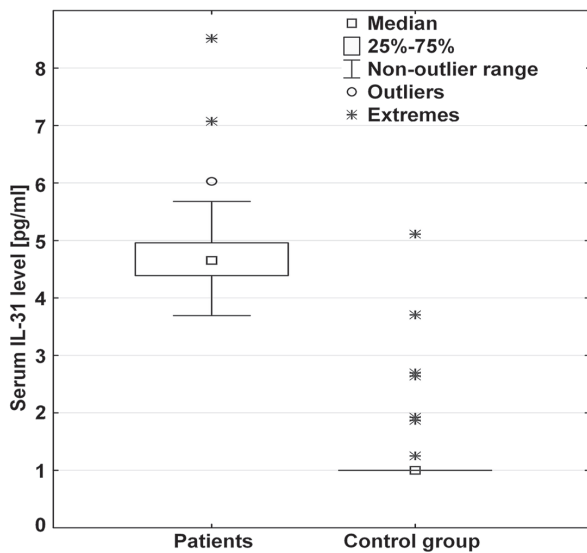


Fig. 1. Serum IL-31 level in cutaneous T-cell lymphomas patients compared to healthy controls ( $p=0.00001$ ).

in stage IB (EM-2.1%, ELB-0%) (EM  $p=0.047$ , ELB  $p=0.043$ ) and than in other stages (IA+IB+IIB+III+IV) (EM-2.4%, ELB-1.2%) (EM  $p=0.017$ , ELB  $p=0.044$ ). In turn, the frequency of haplotype AGA for the IL-31 gene was statistically lower in stage IA (ELB-9.5%) than in other stages (ELB-28.0%) (ELB  $p=0.021$ ) (Table SII<sup>1</sup>).

#### Serum IL-31 level and pruritus in relation to genetic variant polymorphisms

There were statistical differences in serum IL-31 levels between genotypes AA and AG ( $p=0.014$ ), between genotypes AA and GG ( $p=0.008$ ) and between genotypes G (+) and G (-) ( $p=0.007$ ) for the -2057 gene polymorphisms. Moreover, the serum IL-31 concentrations were statistically higher in patients with genotype GG compared to AA for the IVS2+12 gene polymorphisms ( $p=0.028$ ) (Tables SIII<sup>1</sup> and SIV<sup>1</sup>). Finally, there were statistically significant differences in serum IL-31 levels between haplotype AGA (+) and AGA (-) (EM  $p=0.019$ ; ELB  $p=0.005$ ) (Tables SV<sup>1</sup> and SVI<sup>1</sup>).

There were no statistically significant differences in pruritus scores between genotypes and haplotypes for the -1066, -2057, IVS2+12 gene polymorphisms (data not shown).

## DISCUSSION

MF and SS, which constitute 70–75% of all CTCL, are known to be associated with significant, distressing pruritus (8–16). To date, only a few studies have addressed the prevalence and severity of this symptom.

Green et al. (29) found that pruritus was not an independent prognostic variable in

the course of CTCL, however the symptom may be associated with the development of sleep disturbances, depression and fatigue.

The analysis of the demographic data of the patients with MF and SS examined here showed strong similarities, in terms of age and sex, to patients treated at the Medical University in Lodz in 1985–2005 (13). The male/female ratio was slightly lower in the analysis performed by Agar et al. (M:F = 1.6) (30).

The mean age at diagnosis was 59 years in our study group. This is consistent with other studies. In the Polish study performed by Lesiak et al. (64 subjects), the mean age of the diagnosis was 60 years (13), and in the analysis carried out by Agar et al. (1,502 patients) the mean age was 54 years (30).

The mean time between the appearance of first skin lesions and diagnosis was 5 years, which was consistent with the study of Demierre et al. (9). Diagnostic problems in CTCL are the result of non-specific skin symptoms in the early stage of disease, which can imitate other disorders such as psoriasis or eczema. Of the patients with MF and SS 67.7% reported pruritus. A similar percentage was noted by Lesiak et al. (13) and Vij & Duvic (10). The percentage of subjects with pruritus was similar to that found in studies in patients with psoriasis (31) and significantly higher than described in acne (32).

The mean pruritus score for all patients was 2.9 (VAS). In the early stages the mean value was 2.6 and in the advanced stages 3.8. Similar VAS values were reported by Wright et al. (8). The observations confirm the reports of other authors, that pruritus is more severe in the late stages (33). The pruritus score was highest in a patient with erythroderma, which is consistent with other studies (12, 15, 16).

The serum IL-31 level in CTCL patients was significantly higher than in the control group. The possible

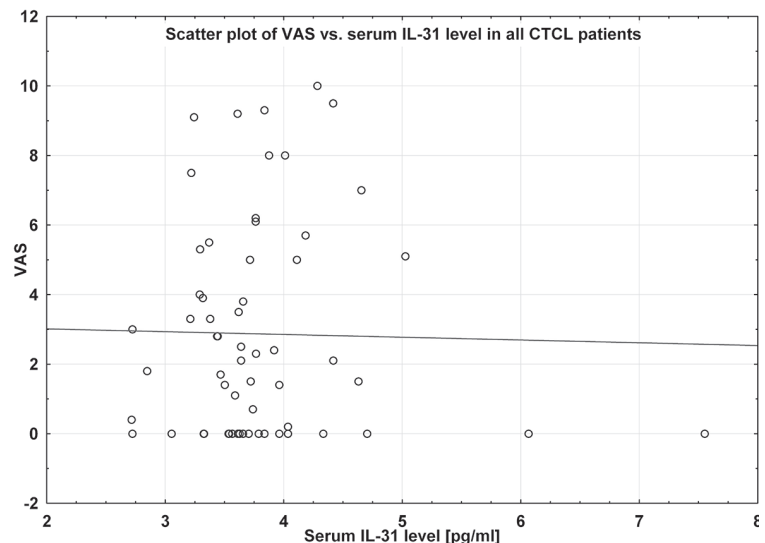


Fig. 2. Lack of correlation between VAS and serum IL-31 level in all cutaneous T-cell lymphomas patients (R-Spearman 0.017,  $p=0.894$ ).



role of IL-31 in the pathogenesis of the disease emerges also from the results presented by Ohmatsu et al. (34) based on a group of 38 patients with CTCL where a significantly higher serum IL-31 level was found in patients with CTCL compared to the control group.

Considering all CTCL patients, there were no correlation between serum IL-31 concentration and pruritus, but a statistically significant relation was demonstrated in patients in stage IB. Singer et al. (26) confirmed higher serum IL-31 levels in cases of pruritic CTCL compared to non-pruritic ones. The high level of IL-31 at the early stages is striking, because of the dominance of Th1 cytokine profile in this period of the disease, while studies in mice and humans showed that IL-31 is mainly but not exclusively secreted by Th2 lymphocytes (17, 35). It seems that in the case of CTCL early stages, the source of this cytokine could be Th1 cells as well as the inflammatory cells such as monocytes. It is known that monocytes, macrophages and dendritic cells produce IL-31 in response to UV and hydrogen peroxide exposure (17, 20). It is likely that there are other factors capable of stimulating the cells to produce IL-31, which requires further study.

The lack of correlation between serum IL-31 concentration and pruritus in the entire studied group of CTCL patients, may indicate that this interleukin is not involved in the pathogenesis of pruritus in CTCL. The observed correlation in stage IB and the results of Singer et al. (26) require follow-up studies on a larger group of patients. It should be noted that the mentioned study from United States, which showed a significantly higher serum IL-31 levels in patients with pruritus than without, was performed in a group consisting mainly of patients with the advanced stages of the disease (26). It seems that Th2 lymphocytes have been the main source of IL-31 in the case of advanced stages. Stott et al. (35) demonstrated also that IL-31 expression is dependent on IL-4, which belong to Th2 cytokines. The elimination of IL-4 from a Th2 environment significantly reduced the expression of IL-31. The same authors also showed the induction of IL-31 by IL-33 (35).

The fact that dendritic cells may be the source of IL-31 (17, 20) raises the hypothesis that IL-31 produced by these cells attracts lymphocytes into the epidermis. Microscopic and immunophenotypic analysis of Pautrier's microabscesses revealed that they are intraepidermal collections of malignant lymphocytes in close association with dendritic cells (36). It can be assumed that the cytokines produced by dendritic cells attract CD4<sup>+</sup> cells to the epidermis, which affects the progression of the disease (37). This can explain differences in results between Singer et al. (26) and our study.

While discussing the possible role of IL-31 in the pathogenesis of MF and SS several aspects should be considered. On one hand, MF share many similarities with inflammatory diseases and mimics them for a long

period of time. On the other hand, this lymphoma has a malignant potential and could behave very aggressively. In addition, the process of T lymphocytes migration into the epidermis remains unclear in details. It is possible that IL-31 is a component of the microenvironment which participates in the extravasation of T cells into the skin (37, 38).

The role of IL-31 in the pathogenesis of diseases has been confirmed in many inflammatory dermatoses, including AD, allergic contact dermatitis and psoriasis (25, 34, 39–43). The increased expression of IL-31 in the skin of transgenic mice correlated with intensity of skin lesions (17, 44). Skin biopsies from patients with AD and prurigo nodularis showed an increased IL-31 level (25, 40). Patients with AD and psoriasis had an elevated IL-31 serum level (34, 39–43, 45, 46).

IL-31 suppresses cell proliferation when the cell density is low and looses antiproliferative activity or even stimulates cell proliferation when the cell density is high at least in a colorectal cancer cell line HTC116 (47). It is likely that additional signals from different cells modulate IL-31 activity in cell proliferation (22). Although recent studies have demonstrated that IL-31 is effective in suppressing the proliferation of lung epithelial cells (48, 49). Furthermore it is known that IL-31 stimulates STAT-3 and STAT-5 (18, 22), by which some cytokines are involved in haematopoiesis (50).

Aforementioned reports have some analogy with CTCL behaviour where initially IL-31, demonstrating the antiproliferative activity, could keep the disease at bay and then lead to uncontrolled growth. Higher levels of IL-31 in stage IA compared to stage IV is however incompatible with the results of studies from Japan. The study performed by Ohmatsu et al. (34) revealed an opposite relationship. This may be caused by a small group of patients in stage IV in our study. In other dermatological diseases, correlation of IL-31 with disease activity has been shown in AD (40–44) and mastocytosis (51). This correlation has not been found in patients with psoriasis (39).

The genetic variant IL-31 polymorphisms in CTCL have not been studied yet. Studies have only been performed in patients with AD, hand eczema and asthma. In the case of AD, Schulz et al. (27) revealed that GAA haplotype predisposes to the development of AD with normal levels of IgE (nonatopic eczema, NAE). Hong et al. (52) showed that the 2 of IL-31 SNPs were not associated with the development of AD with elevated IgE (atopic eczema, AE), which suggests a connection with NAE. In turn, Lan et al. (53) demonstrated a relationship between specific alleles of IL-31 and AD, but not with non-atopic hand dermatitis. Moreover, Sokołowska-Wojdyło et al. (46) demonstrated that specific alleles and genotypes of the genetic variant IL-31 polymorphisms are more common in patients with AD than in healthy controls and are a risk factor for AD development. There were

no difference in the frequency of alleles and genotypes genetic variant IL-31 polymorphisms between patients with asthma and healthy controls (54).

In view of the fact that AD and CTCL have many similarities, such as eosinophilia, elevated IgE level (34), and the observation that severe AD is a risk factor of lymphomas (55), it seemed that the study of the genetic variant IL-31 polymorphisms in CTCL, proposed by Schulz et al. (27) should find individuals who are predisposed to developing CTCL as well as to find the factors which may indicate the progression when the disease has already been diagnosed.

No differences in allele and genotype frequencies between CTCL and control group have been found. This observation suggests a lack of association between genetic variant IL-31 polymorphisms and the development of CTCL.

There was a significant difference in the frequency of alleles at a locus IVS2+12 between patients in the early and advanced stages. Allele A IVS2+12A/G locus was more frequent in patients in the advanced stages and could be a factor contributing to tumour progression. Differences in the frequency of haplotypes between stage IA and others were also shown, which could serve at the beginning of the disease as an indicator how a patient will progress in the future.

As far as the course of the disease is considered, significant differences are noticeable in the "aggressiveness" between individual patients. Studies have shown that patients with stage IA have a life expectancy comparable to the control population and over 90% of them will not go into more advanced stages (30, 56). The presence of GAG haplotype may be a good prognostic factor, "protecting" patients from disease progression. The presence of AGA haplotype may indicate that the disease may progress in the future.

Statistically, differences in the serum IL-31 levels between patients with specific genotypes and haplotypes are difficult to interpret. Long-term observation of these patients should be undertaken. Perhaps specific genotypes and haplotypes of genetic variant IL-31 polymorphisms, which demonstrated higher levels of IL-31, mark a more rapid progression of the disease. The genetic variant IL-31 polymorphisms studies performed in CTCL are unique and important, however, this requires further investigation.

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#### REFERENCES

- Burg G, Kempf W, Cozzio A, Feit J, Willemze R, S Jaffe E, et al. WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. *J Cutan Pathol* 2005; 32: 647–674.
- Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011; 117: 5019–5032.
- Yamashita T, Abbade LP, Marques ME, Marques SA. Mycosis fungoides and Sézary syndrome: clinical, histopathological and immunohistochemical review and update. *An Bras Dermatol* 2012; 87: 817–828.
- Sokołowska-Wojdyło M, Roszkiewicz J. [Primary cutaneous lymphomas.] Lublin: Czelej, 2008 (in Polish).
- Requena L, González-Guerra E, Angulo J, DeVore AE, Sanguenza OP. Anetodermic mycosis fungoides: a new clinicopathological variant of mycosis fungoides. *Br J Dermatol* 2008; 158: 157–162.
- Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeflner AC, Stevens S, et al. Defining early mycosis fungoides. *J Am Acad Dermatol* 2005; 53: 1053–1063.
- Imam MH, Shenoy PJ, Flowers CR, Phillips A, Lechowicz MJ. Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. *Leuk Lymphoma* 2013; 54: 752–759.
- Wright A, Wijeratne A, Hung T, Gao W, Whittaker S, Morris S. Prevalence and severity of pruritus and quality of life in patients with cutaneous T-cell lymphoma. *J Pain Symptom Manage* 2013; 45: 114–119.
- Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer* 2006; 107: 2504–2511.
- Vij A, Duvic M. Prevalence and severity of pruritus in cutaneous T cell lymphoma. *Int J Dermatol* 2012; 51: 930–934.
- Gerami P, Rosen S, Kuzel T, Boone SL, Guitart J. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. *Arch Dermatol* 2008; 144: 738–746.
- Winkelmann RK, Caro WA. Current problems in mycosis fungoides and Sézary syndrome. *Annu Rev Med* 1977; 28: 251–269.
- Lesiak A, Sobolewska D, Sysa-Jędrzejowska A, Narbutt J. [Retrospective analysis of clinical manifestation in patients with primary cutaneous lymphomas.] *Przegl Dermatol* 2011; 98: 13–18 (in Polish).
- Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood* 2007; 109: 31–39.
- Ahern K, Gilmore ES, Poligone B. Pruritus in cutaneous T-cell lymphoma: a review. *J Am Acad Dermatol* 2012; 67: 760–768.
- Meyer N, Paul C, Misery L. Pruritus in cutaneous T-cell lymphomas: frequent, often severe and difficult to treat. *Acta Derm Venereol* 2010; 90: 12–17.
- Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004; 5: 752–760.
- Cornelissen C, Lüscher-Firzlaff J, Baron JM, Lüscher B. Signaling by IL-31 and functional consequences. *Eur J Cell Biol* 2012; 91: 552–566.
- Ishii T, Wang J, Zhang W, Mascarenhas J, Hoffman R, Dai Y, et al. Pivotal role of mast cells in pruritogenesis in patients with myeloproliferative disorders. *Blood* 2009; 113: 5942–5950.
- Cornelissen C, Brans R, Czaja K, Skazik C, Marquardt Y, Zwadlo-Klarwasser G, et al. Ultraviolet B radiation and reactive oxygen species modulate interleukin-31 expression in T lymphocytes, monocytes and dendritic cells. *Br J Dermatol* 2011; 165: 966–975.
- Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type

- cytokine signalling and its regulation. *Biochem J* 2003; 374: 1–20.
22. Zhang Q, Putheti P, Zhou Q, Liu Q, Gao W. Structures and biological functions of IL-31 and IL-31 receptors. *Cytokine Growth Factor Rev* 2008; 19: 347–356.
  23. Diveu C, Lelièvre E, Perret D, Lak-Hal AH, Froger J, Guillet C. GPL, a novel cytokine receptor related to GP130 and leukemia inhibitory factor receptor. *J Biol Chem* 2003; 278: 49850–49859.
  24. Ghilardi N, Li J, Hongo JA, Yi S, Gurney A, de Sauvage FJ. A novel type I cytokine receptor is expressed on monocytes, signals proliferation, and activates STAT-3 and STAT-5. *J Biol Chem* 2002; 277: 16831–16836.
  25. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; 117: 411–417.
  26. Singer EM, Shin DB, Nattkemper LA, Benoit BM, Klein RS, Didigu CA, et al. IL-31 is produced by the malignant T-cell population in cutaneous T-cell lymphoma and correlates with CTCL pruritus. *J Invest Dermatol* 2013; 133: 2783–2785.
  27. Schulz F, Marenholz I, Fölster-Holst R, Chen C, Sternjak A, Baumgrass R. A common haplotype of the IL-31 gene influencing gene expression is associated with nonatopic eczema. *J Allergy Clin Immunol* 2007; 120: 1097–1102.
  28. Excoffier L, Laval G, Schneider S. Arlequin (version 3.0): an integrated software package for population genetics data analysis. *Evol Bioinform Online* 2005; 1: 47–50.
  29. Green SB, Byar DP, Lamberg SI. Prognostic variables in mycosis fungoides. *Cancer* 1981; 47: 2671–2677.
  30. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010; 28: 4730–4739.
  31. Gupta MA, Gupta AK, Kirkby S, Weiner HK, Mace TM, Schork NJ, et al. Pruritus in psoriasis. A prospective study of some psychiatric and dermatologic correlates. *Arch Dermatol* 1988; 124: 1052–1057.
  32. Reich A, Trybucka K, Tracinska A, Samotij D, Jasiuk B, Srama M. Acne itch: do acne patients suffer from itching? *Acta Derm Venereol* 2008; 88: 38–42.
  33. Suga H, Sugaya M, Miyagaki T, Ohmatsu H, Fujita H, Kagami S, et al. Association of nerve growth factor, chemokine (C-C motif) ligands and immunoglobulin E with pruritus in cutaneous T-cell lymphoma. *Acta Derm Venereol* 2013; 93: 144–149.
  34. Ohmatsu H, Sugaya M, Suga H, Morimura S, Miyagaki T, Kai H. Serum IL-31 levels are increased in patients with cutaneous T-cell lymphoma. *Acta Derm Venereol* 2012; 92: 282–283.
  35. Stott B, Lavender P, Lehmann S, Pennino D, Durham S, Schmidt-Weber CB. Human IL-31 is induced by IL-4 and promotes TH2-driven inflammation. *J Allergy Clin Immunol* 2013; 132: 446–454.
  36. Edelson RL. Cutaneous T cell lymphoma: the helping hand of dendritic cells. *Ann N Y Acad Sci* 2001; 941: 1–11.
  37. Wong HK, Mishra A, Hake T, Porcu P. Evolving insight in the pathogenesis and therapy of cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome). *Br J Haematol* 2011; 155: 150–166.
  38. Sokołowska-Wojdyło M, Jankowska-Konsur A, Grzanka A, Maciejewska-Radomska A. [Pathogenesis of mycosis fungoides and Sézary syndrome.] *Przegl Dermatol* 2012; 99: 235–240 (in Polish).
  39. Narbutt J, Olejniczak I, Sobolewska-Sztychny D, Sysa-Jedrzejowska A, Słowik-Kwiatkowska I, Hawro T, et al. Narrow band ultraviolet B irradiations cause alteration in interleukin-31 serum level in psoriatic patients. *Arch Dermatol Res* 2013; 305: 191–195.
  40. Kim S, Kim HJ, Yang HS, Kim E, Huh IS, Yang JM. IL-31 serum protein and tissue mRNA levels in patients with atopic dermatitis. *Ann Dermatol* 2011; 23: 468–473.
  41. Raap U, Wiczorek D, Gehring M, Pauls I, Ständer S, Kapp A, et al. Increased levels of serum IL-31 in chronic spontaneous urticaria. *Exp Dermatol* 2010; 19: 464–466.
  42. Raap U, Wichmann K, Bruder M, Ständer S, Wedi B, Kapp A, et al. Correlation of IL-31 serum levels with severity of atopic dermatitis. *J Allergy Clin Immunol* 2008; 122: 421–423.
  43. Ezzat MH, Hasan ZE, Shaheen KY. Serum measurement of interleukin-31 (IL-31) in paediatric atopic dermatitis: elevated levels correlate with severity scoring. *J Eur Acad Dermatol Venereol* 2011; 25: 334–339.
  44. Takaoka A, Arai I, Sugimoto M, Honma Y, Futaki N, Nakamura A, et al. Involvement of IL-31 on scratching behavior in NC/Nga mice with atopic-like dermatitis. *Exp Dermatol* 2006; 15: 161–167.
  45. Raap U, Weißmantel S, Gehring M, Eisenberg AM, Kapp A, Fölster-Holst R. IL-31 significantly correlates with disease activity and Th2 cytokine levels in children with atopic dermatitis. *Pediatr Allergy Immunol* 2012; 23: 285–288.
  46. Sokołowska-Wojdyło M, Gleń J, Zabłotna M, Rębała K, Sikorska M, Florek A, et al. Association of distinct IL-31 polymorphisms with pruritus and severity of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2013; 27: 662–664.
  47. Dambacher J, Beigel F, Seiderer J, Haller D, Göke B, Auernhammer CJ, et al. Interleukin 31 mediates MAP kinase and STAT1/3 activation in intestinal epithelial cells and its expression is upregulated in inflammatory bowel disease. *Gut* 2007; 56: 1257–1265.
  48. Chattopadhyay S, Tracy E, Liang P, Robledo O, Rose-John S, Baumann H. Interleukin-31 and oncostatin-M mediate distinct signaling reactions and response patterns in lung epithelial cells. *J Biol Chem* 2007; 282: 3014–3026.
  49. Jawa RS, Chattopadhyay S, Tracy E, Wang Y, Huntoon K, Dayton MT. Regulated expression of the IL-31 receptor in bronchial and alveolar epithelial cells, pulmonary fibroblasts, and pulmonary macrophages. *J Interferon Cytokine Res* 2008; 28: 207–219.
  50. Broxmeyer HE, Li J, Hangoc G, Cooper S, Tao W, Mantel C. Regulation of myeloid progenitor cell proliferation/survival by IL-31 receptor and IL-31. *Exp Hematol* 2007; 35: 78–86.
  51. Hartmann K, Wagner N, Rabenhorst A, Pflanz L, Leja S, Förster A, et al. Serum IL-31 levels are increased in a subset of patients with mastocytosis and correlate with disease severity in adult patients. *J Allergy Clin Immunol* 2013; 132: 232–235.
  52. Hong CH, Yu HS, Ko YC, Chang WC, Chuang HY, Chen GS, et al. Functional regulation of interleukin-31 production by its genetic polymorphism in patients with extrinsic atopic dermatitis. *Acta Derm Venereol* 2012; 92: 430–432.
  53. Lan CC, Tu HP, Wu CS, Ko YC, Yu HS, Lu YW, et al. Distinct SPINK5 and IL-31 polymorphisms are associated with atopic eczema and non-atopic hand dermatitis in Taiwanese nursing population. *Exp Dermatol* 2011; 20: 975–979.
  54. Yu JI, Han WC, Yun KJ, Moon HB, Oh GJ, Chae SC. Identifying polymorphisms in IL-31 and their association with susceptibility to asthma. *Korean J Pathol* 2012; 46: 162–168.
  55. Arellano FM, Wentworth CE, Arana A, Fernández C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007; 127: 808–816.
  56. Kim YH, Jensen RA, Watanabe GL, Varghese A, Hoppe RT. Clinical stage IA (limited patch and plaque) mycosis fungoides. A long-term outcome analysis. *Arch Dermatol* 1996; 132: 1309–1313.