

CLINICAL MANIFESTATIONS AND IMMUNOLOGY OF NUMMULAR ECZEMA

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Being a relatively common chronic skin condition with understudied pathogenesis, nummular eczema captures attention of medical researchers. The aim of this work was to describe clinical manifestations of the disease, revise criteria for its accurate diagnosis and understand the role of malfunctioning components of the adaptive and innate immunities in triggering the inflammatory response. Using high-sensitivity ELISA assays, we assessed the cytokine profiles, determined the levels of adhesion molecules and the affinity of serum antibodies in 51 patients with nummular eczema. The immune profiles of the patients were dominated by proinflammatory interleukins, being deficient in regulatory cytokines. The relative abundance of mononuclear CD50⁺ and CD54⁺ cells was increased. Natural antibacterial immunity was weakened by the production of low-affinity serum antibodies. Based on our findings, we have established criteria for the differential diagnosis of nummular eczema and described a contribution of both regulatory and effector immunity components to the abnormal immune homeostasis. We conclude that the discovered defects of the humoral regulation and non-specific resistance in patients with nummular eczema are pathogenic and determine the course of the disease.

Keywords: nummular eczema, clinical manifestations, interleukins, IL-10, IL-12, IL-17, proinflammatory cytokines, adhesion molecules, antibody affinity, diagnostic criteria, indirect immunofluorescence

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Received: 05.02.2018 **Accepted:** 16.02.2018

DOI: 10.24075/brsmu.2018.006

КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ
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Широкая распространенность, длительное хроническое течение заболевания и недостаточно изученный патогенез определяют интерес к проблеме нуммулярной экземы. Целью настоящего исследования было изучение особенностей клинического течения экземы, клинических критериев для постановки диагноза и определение роли нарушений основных систем врожденного и адаптивного иммунитета в развитии воспалительного процесса. С использованием высокочувствительного ИФА для определения цитокинового статуса, молекул адгезии и аффинности сывороточных антител обследован 51 больной нуммулярной экземой. Установлено, что у больных нуммулярной экземой наблюдались изменение соотношения выработки интерлейкинов с преобладанием провоспалительных вариантов, а также дисбаланс в системе иммунорегуляторных цитокинов. Обнаружен значительный рост относительного количества мононуклеарных клеток CD50⁺ и CD54⁺. Выявлены нарушения естественного антибактериального иммунитета, которые обусловлены продукцией низкоаффинных сывороточных антител. Проведенная работа позволила установить критерии дифференциальной диагностики нуммулярной экземы. Определены особенности нарушений со стороны иммунного гомеостаза, касающиеся как иммунорегуляторных, так и иммуноэффektorных звеньев. Обнаруженные нарушения в системе гуморальной регуляции иммунного ответа и состоянии неспецифической резистентности у больных нуммулярной экземой имеют патогенетическое значение и определяют особенности клинического течения данного заболевания.

Ключевые слова: нуммулярная экзема, клинические проявления, интерлейкины IL-10, IL-12 и IL-17, молекулы адгезии, аффинность антител, диагностические критерии, непрямая иммунофлюоресценция

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Статья получена: 05.02.2018 **Статья принята к печати:** 16.02.2018

DOI: 10.24075/vrgmu.2018.006

Eczema, a common skin condition, remains a therapeutic challenge due to its chronicity, frequent and continuous relapses, understudied pathogenesis and complicated treatment [1–3]. One of eczema types, nummular dermatitis, has been recently reported to become increasingly incident and resistant to standard therapies. To date, eczema is believed to be a polyetiologic disease caused by a variety of overlapping exogenous and endogenous factors [4–6]. Among the major contributors that trigger eczema development and maintain chronic inflammation are endocrine, metabolic and neurohumoral factors and genetic predisposition [7–9]. Some

authors point to the suppressed immunoregulatory function, deficit of regulatory T cells and increased activity of humoral immunity that accompany nummular eczema, suggesting that abnormalities in both cellular and humoral components of the immune system may have a role in the development of this disease and its relapses [10–13].

It has been established that non-specific resistance and functional activity of neutrophils are often compromised in patients with nummular eczema; their complement system is dysfunctional, lipid peroxidation is aggravated and the compensatory antioxidant system is hyperactive [14, 15]. On

the whole, though, cytokine profiles of such patients have hardly been investigated. The literature is scarce [10] and does not give a full picture of how cytokines are involved in this pathology. With that in mind, we decided to study how proinflammatory IL-17 and regulatory IL-10 and IL-12 behave in patients with nummular eczema.

Our aim was to describe clinical manifestations specific for nummular eczema and understand the roles of defective interleukin-based modulation of the immune response and non-specific resistance in the development of this condition.

METHODS

The study was carried out at the facilities of Cheryomushinsky Moscow Research and Clinical Center for Dermatology, Venereology and Cosmetology of Moscow Department of Healthcare. The study was approved by the local Ethics Committee of Pirogov Russian National Research Medical University, Protocol № 164 dated April 17, 2017. All patients gave informed consent to participate. The study was conducted in patients over 18 years of age who had developed clinical symptoms of nummular eczema more than 6 months before the study and had not been receiving immunosuppressive drugs in the last 6 months before the study. The exclusion criteria were severe chronic conditions, TB, syphilis, cancer, and refusal to participate.

The participants included 23 males and 28 females aged 18 to 64 years. The onset of the disease varied considerably, occurring on average 4.8 ± 0.4 years before the study.

In most cases, the first clinical symptoms appeared between 18 to 28 years of age. The most common triggers were household irritants (10 patients, or 19.6%), stress (9 patients, or 17.6%), and diet (6 patients, or 11.8%). Microbial contamination was observed in all participants and was chronic and recurrent in 44 patients (86.3%). The number of relapses varied from 2 to 8 per year, lasting from 2–3 weeks to 3 months. The symptoms were very pronounced, indicating acute inflammation. Twenty-one patients (41.2%) had lesions on upper and lower extremities (the back of the hands, soles, forearms and lower legs). Other patients (58.8%) had extensive cutaneous lesions on the back, shoulders, lateral body surfaces and abdomen. The disease started with itchy round-shaped erythematous spots with clear boundaries, miliary or vesicular papules, pustules, crusting and scaling. In rare cases patients developed microvesicles, followed by the formation of serous wells and oozing.

Using ELISA assays, we measured the levels of IL-10, IL-12 and IL-17 in the patients' blood serum. The tests were performed using the Proplan microplate washer (Picon, Russia), the SkyLine shaker (ELMI, Latvia) and the Uniplan spectrophotometer (Picon, Russia). Reagent kits were by Vector-Best, Russia.

Peripheral blood mononuclear cells were immunotyped by indirect immunofluorescence using ICO monoclonal antibodies. The relative antibody affinity was determined by solid phase immunoassays with different molar concentrations of sodium thiocyanate, which breaks the bonds in the antigen-antibody complex. The levels of soluble antigens sCD50 and sCD54 were measured by ELISA using monoclonal antibodies ICO-60 and ICO-184. The obtained concentrations were presented in arbitrary units per ml (U/ml) and compared to the average results of laboratory tests conducted in healthy individuals. The data were processed by variance analysis in Microsoft Excel. Mean arithmetic M and mean error m were computed. Significance of differences was assessed using Student's

t-test. The differences were significant at $p < 0.05$ (95% probability).

RESULTS

The tests revealed elevated concentrations of IL-12 in the peripheral blood of patients with nummular eczema, which were as high as 159.8 ± 5.9 pg/ml in comparison with the reference values (32.1 ± 2.6 pg/ml). The IL-17 levels were elevated in all patients, reaching 6.1 ± 1.0 pg/ml, which was well above the reference range (0.22 ± 0.1 pg/ml). The IL-10 levels were as low as 4.1 ± 0.18 pg/ml, which is substantially below the reference values (14.1 ± 0.2 pg/ml; see the Table). The levels of sCD50 and sCD54 (196.5 ± 4.6 U/ml and 31.5 ± 2.8 U/ml, respectively) fell outside the reference range, but the difference was minor. Still, the relative quantities of mononuclear cells CD50⁺ and CD54⁺ ($79.8 \pm 9.9\%$ and $81.8 \pm 10.8\%$, respectively) in the blood serum of the participants were significantly above the norm ($59.3 \pm 7.8\%$ and $60.2 \pm 7.9\%$, respectively). The analysis of the immunoassay data showed reduced affinity of serum antibodies to the common antigenic determinant in 26 (51.1%) patients with nummular eczema. Normal affinity was observed in 25 (49.9%) patients. Reduction to 500–1000 units was observed in 16 (31.4%), reduction below 500 units – in 10 (19.7%) patients.

DISCUSSION

The symptoms of nummular eczema have changed significantly over the years complicating differential diagnosis and affecting diagnostic accuracy. The typical location of lesions is now different, their pattern tending to be infiltrative, with rare exuding vesicles or microerosions.

The conducted immunoassays have demonstrated that the onset and development of nummular eczema are accompanied by immunological events typical for acute inflammation. The literature [2] mostly reports abnormal production of IL-1, IL-2 and IL-6. Our study, however, provides a more objective picture of cytokine behavior in patients with nummular eczema. Specifically, we have established a multifold increase in IL-12 and IL-17, indicating a tendency of lymphocytes to differentiate more into Th1 than into Th0 cells, which probably results in intense production of proinflammatory cytokines and triggers acute inflammatory response in the dermis and epidermis. In turn, the lack of IL-10 leads to the immunoregulatory dysfunction and promotes pathological changes that determine the clinical symptoms of the disease. A huge increase in low-affinity antibodies downregulates the activity of the complement system and facilitates microbial opsonization, eliminating the bacterial threat. At the same time, low-affinity antibodies bind to the membrane receptors of regulatory T cells making them more sensitive to microbial antigens. The number of soluble adhesion molecules falls, while their membrane-bound forms

Table 1. Cytokine concentrations in the blood serum of patients with nummular eczema

	IL-10 (pg/ml)	IL-12 (pg/ml)	IL-17 (pg/ml)
Patients with nummular eczema (n = 38)	$4.1 \pm 0.18^*$	$159.8 \pm 5.9^*$	$6.1 \pm 1.0^*$
Reference values	14.1 ± 0.2	32.1 ± 2.6	0.22 ± 0.1

Note: *significant at $p < 0.01$, as compared to the reference values.

become abundant, contributing to the increased migration of cells to the inflammation sites and promoting chronicity.

CONCLUSIONS

Our study reveals that these days the symptoms of nummular eczema start to show at a young age, the typical location of

lesions is different, and exudating microvesicles, vesicular papules, microerosions, and oozing are rare.

We have demonstrated the role of imbalanced levels of cytokines and adhesion molecules in the formation of the pathologic immune response in patients with nummular eczema. Increased production of low-affinity antibodies suggests compromised natural antibacterial immunity.

References

- Orkin VF, Olekhovich RM. Mikrobnaya ekzema (klinika, patogenez, lecheniye). *Dermatovenerologiya i kosmetologiya*. 2002; (2): 24–6.
- Poudel RR, Belbase B, Kafle NK. Nummular eczema. *J Community Hosp Intern Med Perspect*. 2015; Jun 15; 5 (3): 27909. DOI:10.3402/jchimp.v5.27909. eCollection.
- Abdrahimova NA, Nadyrchenko RM, Mustafina GR, Hismatullina ZP, Zaharchenko VD. `Effektivnost' traditsionnoj terapii pri mikrobnnoj `ekzeme. *Meditinskij vestnik Bashkortostana*. 2013; 8 (4): 27–9.
- Legesse Dorsissa Gobena, Prokhorenkov VI. On the pathogenesis of eczema (literature review). *Siberian medical review*. 2003, 1 (25): 65–7.
- Halberg M. Nummular eczema. *J Emerg Med*. 2012; 43 (5): 327–8.
- Iliev D, Niedner R. Diagnosis of eczema. Can you recognize what your patient's symptom? *MMW Fortschr Med*. 2001; Jun 14; 143 (24): 30–3. German.
- Brown SJ. Molecular mechanisms in atopic eczema: insights gained from genetic studies. *J Pathol*. 2017; 241 (2): 140–5.
- Karakaeva AV, Utts SP. Rol' narushenij `epidermal'nogo bar'era v patogeneze `ekzemy (obzor). *Saratovskij nauchno-meditinskij zhurnal*. 2014. 10 (3): 525–30.
- Kim WJ, Ko HC, Kim MB, Kim DW, Kim JM, Kim BS. Features of *Staphylococcus aureus* colonization in patients with nummular eczema. *Br J Dermatol*. 2013 Mar; 168 (3): 658–60. DOI: 10.1111/j.1365-2133.2012.11072.x.
- Abdrahimova NA, Mustafina GR, Hismatullina ZR, Zaharchenko VD. Immunological concept of the development of microbial eczema. *Medical journal of Bashkortostan*. 2014, 9 (1): 109–16.
- Abdrahimova NA, Nadyrchenko RM, Mustafina GR, Hismatullina ZP. Sravnitel'nyj analiz funkcional'noj aktivnosti nejtrofilov venoznoj krovi i iz ochaga vospaleniya pri mikrobnnoj `ekzeme. *Prakticheskaja meditsina*. 2013; 1–4 (73): 58–61.
- Järvikallio A, Harvima IT, Naukkarinen A. Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Arch Dermatol Res*. 2003; Apr; 295 (1): 2–7. Epub 2003 Jan 31.
- Roberts H, Orchard D. Methotrexate is a safe and effective treatment for paediatric discoid (nummular) eczema: a case series of 25 children. *Australas J Dermatol*. 2010; May; 51 (2): 128–30. DOI: 10.1111/j.1440-0960.2010.00634.x.
- Nagoev BS, Nal'chikova MT. Osobennosti perekisnogo okisleniya lipidov u bol'nyh `ekzemoj. *Kubanskij nauchno-meditinskij vestnik*. 2012; 4 (133): 74–5.
- Nikonova IV, Orlov EV, Konnov PE. Sostojanie biotsenoza kozhi pri mikrobnnoj `ekzeme. *Prakticheskaja meditsina*. 2011; 2 (49): 80–2.

Литература

- Оркин В. Ф., Олехнович Р. М. Микробная экзема (клиника, патогенез, лечение). *Дерматовенерология и косметология*. 2002; (2): 24–6.
- Poudel RR, Belbase B, Kafle NK. Nummular eczema. *J Community Hosp Intern Med Perspect*. 2015; Jun 15; 5 (3): 27909. DOI: 10.3402/jchimp.v5.27909. eCollection.
- Абдрахимова Н. А., Надырченко Р. М., Мустафина Г. Р., Хисматуллина З. П., Захарченко В. Д. Эффективность традиционной терапии при микробной экземе. *Медицинский вестник Башкортостана*. 2013; 8 (4): 27–9.
- Легессе Дорсисса Гобена, Прохоренков В. И. О патогенезе экземы (обзор литературы). *Сибирское медицинское обозрение*. 2003; (1): 65–7.
- Halberg M. Nummular eczema. *J Emerg Med*. 2012; 43 (5): 327–8.
- Iliev D, Niedner R. Diagnosis of eczema. Can you recognize what your patient's symptom? *MMW Fortschr Med*. 2001; Jun 14; 143 (24): 30–3. German.
- Brown SJ. Molecular mechanisms in atopic eczema: insights gained from genetic studies. *J Pathol*. 2017; 241 (2): 140–5.
- Каракеева А. В., Утц С. П. Роль нарушений эпидермального барьера в патогенезе экземы (обзор). *Саратовский научно-медицинский журнал*. 2014; 10 (3): 525–30.
- Kim WJ, Ko HC, Kim MB, Kim DW, Kim JM, Kim BS. Features of *Staphylococcus aureus* colonization in patients with nummular eczema. *Br J Dermatol*. 2013; Mar; 168 (3): 658–60. DOI: 10.1111/j.1365-2133.2012.11072.x.
- Абдрахимова Н. А., Мустафина Г. Р., Хисматуллина З. П., Захарченко В. Д. Иммунологическая концепция развития микробной экземы. *Медицинский вестник Башкортостана*. 2014; 9 (1): 109–16.
- Абдрахимова Н. А., Надырченко Р. М., Мустафина Г. Р., Хисматуллина З. П. Сравнительный анализ функциональной активности нейтрофилов венозной крови и из очага воспаления при микробной экземе. *Практическая медицина*. 2013; 1–4 (73): 58–61.
- Järvikallio A, Harvima IT, Naukkarinen A. Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Arch Dermatol Res*. 2003; Apr; 295 (1): 2–7. Epub 2003 Jan 31.
- Roberts H, Orchard D. Methotrexate is a safe and effective treatment for paediatric discoid (nummular) eczema: a case series of 25 children. *Australas J Dermatol*. 2010; May; 51 (2): 128–30. DOI: 10.1111/j.1440-0960.2010.00634.x.
- Ногоев Б. С., Нальчикова М. Т. Особенности перекисного окисления липидов у больных экземой. *Кубанский научно-медицинский вестник*. 2012; 4 (133): 74–5.
- Никонова И. В., Орлов Е. В., Коннов П. Е. Состояние биоценоза кожи при микробной экземе. *Практическая медицина*. 2011; 2 (49): 80–2.