

S. N. Nedelska^{1,2}, O. P. Pakholchuk^{1,2}**An 8-month old with erythema nodosum – clinical case report**¹University Hospital of Zaporizhzhia State Medical University,²Zaporizhzhia State Medical University**Key words:** *Erythema nodosum, Children, Food Allergy, Specific IgE, Gluten.*

Erythema nodosum is rare pathology in childhood and usually associated with big antigen load.

Aim of the work was to make differential analysis of the described case with developed multiple, nontender, depth erythematose papules in the epidermis-dermis (like nodules) on the head, trunk, extremities, associated with adopted cow's milk-based formula intake.

Methods and results. The next methods, as deep literature review and differential analysis, helped to underline probable pathogenetic mechanisms of such type of allergy skin symptoms, to diagnose Erythema nodosum in the child.

Conclusion. This clinical case showed presence of rare clinical food allergy skin symptoms that have mixed mechanisms of onset. Further studies of the gear of onset and histology specificity are needed.

Вузлувата еритема у 8-місячної дитини – клінічний випадок

С. М. Недельська, О. П. Пахольчук

Вузлувата еритема – рідкісна патологія, що виникає в дитячому віці, як правило, пов'язана із великим антигенним навантаженням. Мета роботи полягала у здійсненні диференційного аналізу описаного випадку множинних нещільних, глибоких еритематозних папул у дермі-епідермісі (вузлуватоподібних), що були розташовані на голові, тулубі, кінцівках у 8-місячної дитини; їхня поява була пов'язана із вживанням сумішей на основі коров'ячого молока. Методами поглибленого літературного огляду, диференційного аналізу встановлено можливі патогенетичні механізми розвитку цього виду алергії, верифікований діагноз вузлуватої еритеми. Клінічний випадок свідчить про наявність рідкісних форм клінічних проявів харчової алергії на шкірі, що мають змішані механізми розвитку. Поглиблене гістологічне обстеження необхідне в перспективі наступних досліджень подібних випадків.

Ключові слова: вузлувата еритема, діти, харчова алергія, специфічний IgE, глютен.

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Узловатая эритема у 8-месячного ребенка – клинический случай

С. Н. Недельская, О. П. Пахольчук

Узловатая эритема – редкая патология, которая возникает в детском возрасте, как правило, связана с большой антигенной нагрузкой. Целью работы было провести дифференцированный анализ описанного случая множественных неуплотненных, глубоких эритематозных папул в дерме-эпидермисе (узловатоподобных), локализирующихся на голове, туловище, конечностях у 8-месячного ребенка; их появление было связано с употреблением смесей на основе коровьего молока. Методами углубленного литературного обзора, дифференцированного анализа установлены возможные патогенетические механизмы развития данного вида аллергии, верифицирован диагноз узловатой эритемы. Данный клинический случай свидетельствует о наличии редких форм клинических проявлений аллергии на коже, которые имеют смешанный механизм развития. Углубленное гистологическое обследование необходимо в перспективе дальнейших исследований подобных случаев.

Ключевые слова: узловатая эритема, дети, пищевая аллергия, специфический IgE, глютен.

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Erythema nodosum (EN) is the most common type of panniculitis; it may be due to a variety of underlying infectious or otherwise antigenic stimuli. The pathogenesis remains to be elucidated. EN can be one of the forms of the allergic vasculitis. Beyond treating underlying triggers, therapeutic options consist mainly of nonsteroidal anti-inflammatory drugs, symptomatic care, potassium iodide, and colchicines [1-3,5,6].

Our **aim** was to present case of the EN like symptoms in infant which are rarely seen in this age.

Case Presentation. An 8-month-old male was seen in the outpatient department of the University Hospital of Zaporizhzhia State Medical University because of the multiple, nontender, depth erythematose papules in the epidermis-dermis (like nodules) over the body, associated with adopted cow's milk-based formula intake. The patient had no history of fever, low appetite, vomiting, or diarrhea. Artificial feeding was started early – on the 3rd week of life due to

the hypogalactia. Several weeks ago easily-digested instant cereal-based preparations were added to the child's menu. Two weeks later, mother noticed first nodules appeared on the face, trunk, extremities and their quantity gradually increased. Lesions onset was sudden and symmetrical. She took the child to pediatrician's office. The mother could recall no specific insect bites to his legs, and that small bumps had not been painful or tender. The patient had been treated with antihistamine medications (Dimetinden maleas, Chloropyramine hydrochloride) without positive effect. At first, the nodules showed bright red color, but within some time, mostly on the shins, they become livid red. The boy was a full-term infant with normal birth weight. No complications were reported with labor or delivery and he has no history of medical problems. Routine immunizations had been administered. There were no relatives with allergic diseases and his family history was unremarkable. The patient was not taking any medications and had no recent illnesses

or sick contacts before and at the time of skin symptoms appearance. He had no exposure to domestic animals and rats. Appetite was good.

On examination, the patient had normal physical and mental development. He had no fever, chills, dysphagia, nausea, abdominal pain, bleeding. His mood was good, and he slept through the night. During exam the boy was alert, occasionally cooperative and playful. The mucous membranes were pink, moist.

There were papules approximately 3 to 5 mm in diameter free within the epidermis and superficial layers of the derma. Their color was deep red, they were firm, spheriform, nontender, slightly mobile. Palpation elicited no discomfort. They were localized over the face, neck, on the lower extremities, mostly on the shins (*Fig. 1 on the color tab №4*). Abdomen, scalp and upper extremities were covered minimally. They were not fixed to skin or subcutaneous tissue below.

Patient had no itching, xerosis, maceration zone. Lymphatic nodules were not enlarged, painless, elastic. Internal organs exam data were normal. He had no hepatosplenomegaly. The stool was regular, 1-2 times per day. Laboratory evaluation showed normal Complete blood count, levels of serum electrolytes and normal results of liver-function tests. Serum level of the anti-CMV IgM and IgG was negative. Serum IgE level was 122,8 IU/ml. Specific IgE levels to *Bovine* serum albumin (29 kU/l), Veal (5.6 kU/l) were elevated (referent range – 0.35kU/l). Specific IgE levels to α -Lactalbumin (0.25kU/l), soy (0.25 kU/l), yeast (0.25kU/l), Birch+Oak (0.25 kU/l), Alder+Hazel (0.25 kU/l) were borderline increased. Specific IgE levels to casein, β -Lactoglobulin, egg, rice, banana, pork, chicken, flour, *D. pteron.*+*D. farinae*, *Cladosp. herb*+*Altern. alter.*, grasses were not changed.

Differential diagnosis. When considering the skin symptoms most important aspects were: the number, firmness, localization, color and absence of itching, and no effect from antihistamine drug. Because the most part of the lesions were on the shin, erythema nodosum was initially considered as a primary diagnosis. It was important to distinguish between infectious, inflammatory and neoplastic causes [1,12]. Multiple causes of EN related to infection have been described, including streptococcal infection, tuberculosis, coccidioidomycosis, and histoplasmosis, as well as infections caused by species of bartonella, yersinia, salmonella, mycoplasma, chlamydia, and leptospira [12]. Acute urticaria, insect bites were included into the differential diagnosis list too.

In infectious EN intoxication and change of the general state of health are usually presented as fever, low appetite, hepatosplenomegaly, CBC change, serum specific antibodies levels. In a special case of leprosy, syphilis and leishmaniasis other specific symptoms are seen as usual [1,2,12]. Our patient didn't have such symptoms. Taking into account situation with tuberculosis the boy's history was additionally analyzed. Patient's parents, the boy were vaccinated with BCG vaccine and had scar on the shoulder. Child's general condition, other organs, except skin, were not affected. Metastatic neuroblastoma was excluded because it is commonly associated with internal organs affection [12].

The patient did not have a recent history of pharyngitis

or scratches, bites. Child and his clothes were carefully examined, other family members were healthy. EN elements did not have any bite signs. Moreover his specific IgG and IgM to Cytomegaloviral infection were studied, result was negative. Important considerations in a young child are lymphoma and sarcoma, which may be presented as multiple cutaneous nodules. But as malignant, as fungal nodules usually have indistinct borders, are often fixed with underlying tissues. They heal with scars. Our patient had mobile nodules, they healed without atrophy or scarring. Acute urticaria was excluded too. No urticaria elements were presented, child didn't have pruritis, pigmentation. *Darier's* sign was negative. There was no effect from the antihistamine drug intake.

EN may be due to a variety of underlying infectious or otherwise antigenic stimuli. Both neutrophilic inflammation and granulomatous inflammation are implicated in the pathogenesis [6,12]. This fact gave us opportunity to suspect non infectious causes of the EN in this case. It was shown that in one third of cases cause of the EN can't be founded [1–3,5]. Patient's history gave us information about possible cause of the disease onset: progression and redness increase was associated with adopted cow's milk-based formula intake. Common clinical signs of food intolerance makes distinguishing immunological and non-immunological mechanisms difficult [10,13]. On the other hand skin symptoms appeared spontaneously only 2–3 weeks before visit to the doctor. In contrast, rather confused was duration of the artificial feeding of the child – about 4-5 months. Because, as usual, milk protein allergy presents from a few days to a few weeks after the introduction of milk protein into the diet. Sensitization period usually takes some time, but can it be about 3–4 months? Additional history data showed that several weeks ago easily-digested instant cereal-based preparations were added to the child's menu. Taking into account literature data about presence of the cross reactivity between milk and wheat proteins, we suspected some contribution of the cereals in the disease onset [9,11]. These facts explained given time frames. The patient had increased serum level of the common IgE and no evidence of inflammation or other abnormalities. Of the diagnoses that remain, food hypersensitivity EN is the most likely. With this disorder all lab data are usually normal except specific and common IgE levels. One needs to consider the skin allergy testing should be done lately because of the age or because of the condition? Specific IgE levels were estimated. It was increased more than in 80 times to cow proteins and in 16 times to meat. It was interesting but patient didn't have elevated IgE to wheat. Based on the results of lab test, the diagnosis of food allergy was made. IgE and non-IgE mechanism were suspected (to milk and wheat correspondently). Amino-acid formulas were prescribed for the patient for 2 weeks with shift to partial hydrolysate. Cereal-Based Gluten-Free Food was prescribed too. For topical use emollient was recommended for frequent application (5–6 times/day). View of the patient's legs is given on the *Fig. 2 on the color tab №4*.

Unfortunately parents refused to make biopsy of the nodules and complete differential diagnosis was not finished. Histiocytoses are a group of disorders involving

the proliferation and accumulation of cells which can have manifestation with polymorphous cutaneous eruption over the whole body. As it was in our patient, the clinical course of Histiocytoses is usually benign and self-limited. The aetiology in paediatrics is still unclear. Virus-induced local immune alternation in the transformation of the histiocytosis has been postulated [4]. But in this case eruption onset was associated with easily-digested instant cereal-based preparations introduce and it increase was associated with adopted cow's milk-based formula intake.

Discussion

In this case, based on the patient's history, on the conditions of resolution of symptoms when adopted cow's milk-based formula was removed, food allergy was suspected. Literature review showed few data concerning EN in children, mostly it related to the hypersensitivity reactions in adults.

Specific clinical skin symptoms and order of their appear made us to suspect EN. N.F. Filatov named this illness «disease in stockings» and our patient had maximal deep papulas/nodules localisation on shins. N.I. Nisevich reported about allergic eruptions looking like EN for differential diagnosis of the infectious diseases [3].

Prof I.V. Bogadelnikov indicated that sizes of the nodules can be from 0.5 to 3 cm, our patient had nodules 0.3–0.5 up to 1 cm. Although he denoted that usually these elements undergo evolution, change color [1]. But our patient's

eruption just gradually disappeared, turned pale. Furthermore Prof I.V. Bogadelnikov indicated that evolution is not permanent and other clinical variant of the EN can be [1].

The one should be noted: patient had painless eruptions, which is usually seen in such kind of the skin disorders. That fact gives opportunity to make concerning about this clinical specificities of the allergic EN in children.

To our mind this patient's food hypersensitivity EN had cell-mediated or mixed IgE- and cell-mediated mechanism of onset. *Habif T. et al. 2011 indicated that EN usually occurs due to the hypersensitivity reactions in the condition of the massive antigen stimuli.* Other systems are not changed, lymphadenopathy can be founded [7]. It is interesting to note that EN in this patient started to recover gradually only after diet correction and emollient applying. Total recover became only in 3 weeks. In such situation gluten hypersensitivity was suspected. G. Kristjánsson et al (2007) showed that mucosal inflammatory response similar to that elicited by gluten was produced by CM protein in about 50% of the patients with coeliac disease [9]. Effectiveness of the recommended diet with amino-acid formula and cereal-based gluten-free food confirmed our suspicion.

This case gave us opportunity to underline EN as probable clinical form of the food allergy with mixed IgE- and nonIgE-mechanism. Further studies of the gear of onset and histology specificity are needed.

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Information about authors:

Nedelska S.M., MD, PhD, Professor, University Hospital of Zaporizhzhia State Medical University, Head of the Department of Faculty Pediatrics, Zaporizhzhia State Medical University.

Pakholchuk O.P., MD, PhD, Associate Professor, University Hospital of Zaporizhzhia State Medical University, Department of Faculty Pediatrics, Zaporizhzhia State Medical University, Ukraine, E-mail: opzgm@rambler.ru.

Відомості про авторів:

Недельська С.М., д. мед. н., професор, Університетська клініка Запорізького державного медичного університету, зав. каф. факультетської педіатрії, Запорізький державний медичний університет.

Пахольчук О.П., к. мед. н., доцент, Університетська клініка Запорізького державного медичного університету, каф. факультетської педіатрії, Запорізький державний медичний університет, E-mail: opzgm@rambler.ru.

Сведения об авторах:

Недельская С.Н., д. мед. н., профессор, Университетская клиника Запорожского государственного медицинского университета, зав. каф. факультетской педиатрии, Запорожский государственный медицинский университет.

Пахольчук О.П., к. мед. н., доцент, Университетская клиника Запорожского государственного медицинского университета, каф. факультетской педиатрии, Запорожский государственный медицинский университет, E-mail: opzgm@rambler.ru.

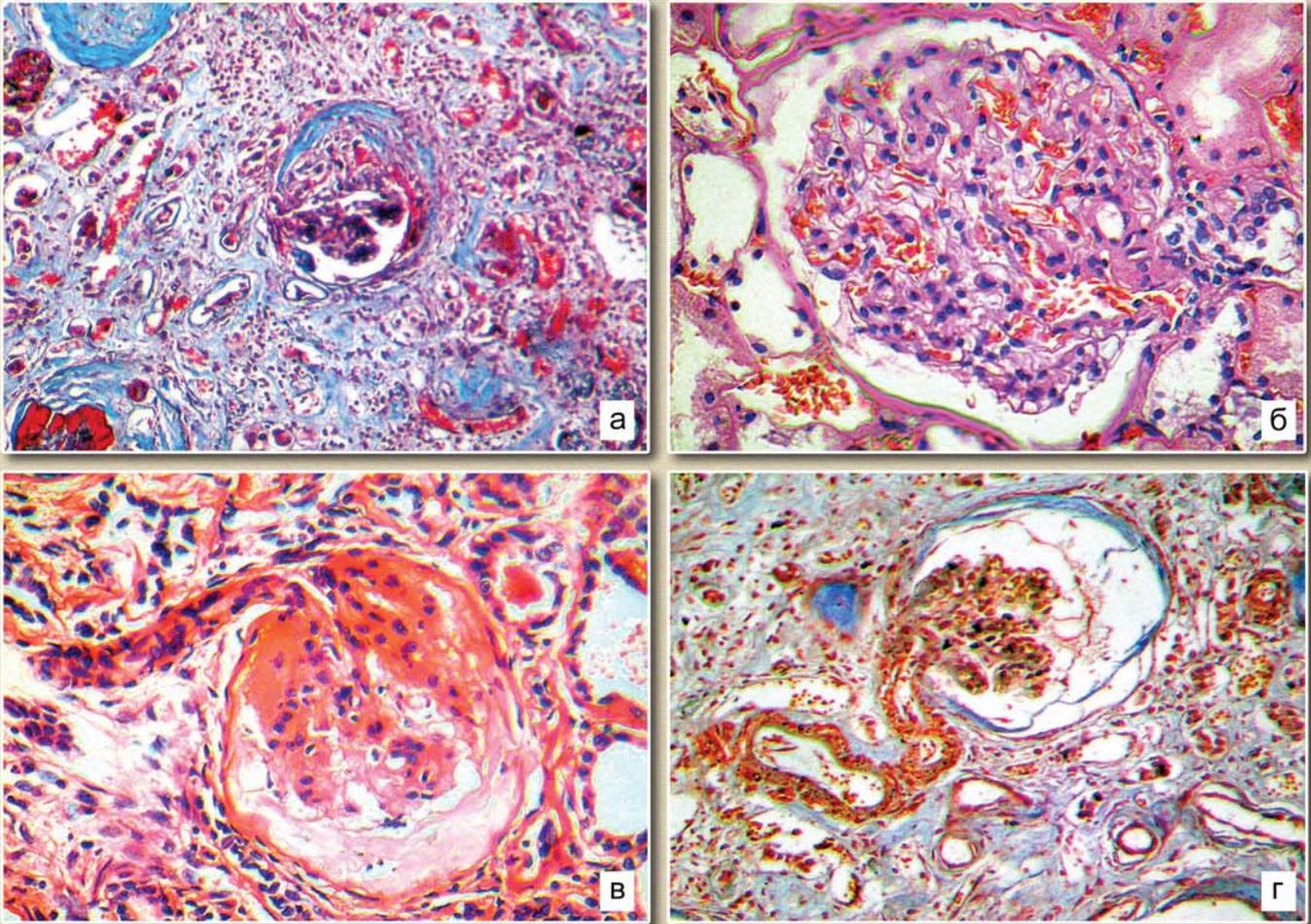


Рис. 1. Ураження нирок при МС: а – гіаліноз, дегенеративні зміни епітеліальних клітин канальців; б – інтеркапілярний вузликівий гломерулосклероз, зрощення капілярних петель з капсулою Боумена; в – гіаліноз клубочка і приносячої артеріоли; г – дистрофічні зміни у гладких м'яцях аферентної артеріоли. Заб.: а, г – за Масоном; б, в – гематоксиліном-еозином. 36.: ок. 10, об. 10.

(Рис. 1 до статті І. В. Козлової «Патоморфологічні особливості ураження нирок в умовах метаболічного синдрому (за даними аутопсій і в експерименті)», с. 81–84)



Figure 1. Area with maximal deep papulas/nodules localisation. Multiple, nontender, depth erythematose papules in the epidermis-dermis (like nodules).



Figure 2. Skin condition after 2 weeks of the treatment.

(Figures 1–2 to the paper S. N. Nedelska, O. P. Pakholchuk «An 8-month old with erythema nodosum – clinical case report, literature review», p. 114–116)