

©Borgis

Justyna Szczęch<sup>1,2</sup>, Monika Matławska<sup>1</sup>, Maja Rutka<sup>1</sup>, \*Adam Reich<sup>1,2</sup>

# Clinical presentation of erythema nodosum

## Obraz kliniczny rumienia guzowatego

<sup>1</sup>Department of Dermatology, Venereology and Allergology, Wrocław Medical University  
Head of Department: Professor Jacek Szepietowski, MD, PhD

<sup>2</sup>Department of Dermatology, University of Rzeszów  
Head of Department: Professor Adam Reich, MD, PhD

### Keywords

erythema nodosum, clinical characteristics, panniculitis

### Słowa kluczowe

rumień guzowaty, charakterystyka kliniczna, zapalenie tkanki podskórnej

### Summary

**Introduction.** Erythema nodosum (EN) is a painful disorder of the subcutaneous layers of fat tissue. It is the most common form of panniculitis. The pathogenesis of EN still remains unknown, although nowadays EN is considered a delayed hypersensitivity reaction to different antigens.

**Aim.** The aim of our study was to characterize the clinical picture of EN.

**Material and methods.** A total of 44 patients were identified and recruited into this study. Data was collected retrospectively based on the medical charts of patients hospitalized because of EN. We have analyzed the data about duration of the disease, the age of the onset of EN and probable trigger factors. All results were analyzed using the software package Statistica® 12.0 (Statsoft, Krakow, Poland).

**Results.** EN was most commonly diagnosed in women ( $n = 38$ ). The female to male ratio was 4.5:1. The underlying cause of EN was established in 70.5% of all cases. Most commonly the presence of typical inflammatory nodules in the course of EN was connected with a common infectious agent, most commonly to streptococcal pharyngitis. Almost all patients ( $n = 42$ , 95.5%) presented inflammatory subcutaneous nodules. Additionally, 45.5% had erythematous-infiltrative lesions and in 8 (18.2%) patients peripheral edemas were observed. 18.2% of patients reported arthralgia. More than half of the patients demonstrated raised level of inflammation markers and 25.0% had leukocytosis.

**Conclusions.** EN is one of the most common form of panniculitis, however, many aspects of its pathology still remains unanswered. Despite it is believed to be a reactive disease, in many cases the disease is considered idiopathic. Further studies on EN are urgently needed to better characterize its pathomechanism and to optimize the treatment of affected patients.

### Streszczenie

**Wstęp.** Rumień guzowaty (ang. *erythema nodosum* – EN) manifestuje się powstawaniem bolesnych guzów zapalnych w obrębie tkanki tłuszczowej. Jest to najczęstsza postać zapalenia tkanki podskórnej. Patogeneza EN pozostaje wciąż nieznaną, chociaż obecnie EN uważa się za opóźnioną reakcję nadwrażliwości na różne antygeny.

**Cel pracy.** Celem badania było scharakteryzowanie klinicznego obrazu EN.

**Materiał i metody.** Do badania włączono 44 pacjentów. Dane uzyskano z historii medycznej pacjentów hospitalizowanych z powodu EN. Przeanalizowano dane dotyczące czasu trwania choroby, wieku rozpoczęcia EN i prawdopodobnych czynników wywołujących. Wszystkie wyniki zostały przeanalizowane przy użyciu pakietu oprogramowania Statistica® 12.0 (Statsoft, Kraków, Polska).

**Wyniki.** EN częściej stwierdzano u kobiet ( $n = 38$ ). Stosunek kobiet do mężczyzn wynosił 4,5:1. Prawdopodobną przyczynę EN ustalono w 70,5% wszystkich przypadków. Najczęściej występowały typowych zapalnych guzów w przebiegu EN połączono z czynnikiem zakaźnym, zwykle z zapaleniem gardła wywołanym przez streptokoki. Prawie wszyscy pacjenci ( $n = 42$ , 95,5%) prezentowali zapalne guzy podskórne. Dodatkowo 45,5% chorych miało zmiany naciekowo-rumieniowe, a u 8 (18,2%) pacjentów obserwowano obrzęki obwodowe. 18,2% chorych zgłaszało bóle stawów. Ponad połowa pacjentów wykazała podwyższony poziom markerów zapalenia, a 25,0% miało leukocytozę.

**Wnioski.** EN jest jedną z najczęstszych postaci zapalenia tkanki podskórnej, jednak wiele aspektów jego patologii pozostaje bez odpowiedzi. Mimo że uważa się, że jest to choroba reaktywna, w wielu przypadkach jest diagnozowana jako idiopatyczna. Konieczne są dalsze badania dotyczące EN, aby lepiej scharakteryzować jego patomechanizm i zoptymalizować leczenie pacjentów.

### Conflict of interest

#### Konflikt interesów

None

Brak konfliktu interesów

### Address/adres:

\*Adam Reich

Zakład i Klinika Dermatologii  
Uniwersytet Rzeszowski  
ul. Szopena 2, 35-055 Rzeszów  
tel. +48 605-076-722  
adamandrzejreich@gmail.com

## INTRODUCTION

Erythema nodosum (EN) is the most common clinicopathologic subtype of panniculitis (1). Typically patients with EN present painful, red, nonulcerative nodules located both in the skin and the subcutaneous tissue (2). Skin lesions tend to be placed symmetrically on the lower extremities, especially on the anterior tibial surface (1). The onset of the disease is most commonly quite rapid, although the nodules are self-limiting. They involute in up to 6 weeks, leaving no scarring, only a bruise-like lesions on affected skin (2). The development of the nodules is preceded by some non-characteristic symptoms, like malaise, cough, fever, arthralgia with or without arthritis and weight loss. These manifestations may be present from one up to three weeks before the first skin lesions (1-3). The rate of EN is one to five per 100,000 persons and it may vary depending on the country. The men-to-women ratio among the adult population is 1:6 (2-4). Most commonly EN affects young women aged 20 to 40 years, although the disease may occur at any age (2). Interestingly, the sex ratio among children is 1:1 (5). The pathophysiology of EN remains largely unknown, albeit it is believed to be a reactive disease to some infections or autoimmune diseases. However, in many cases of EN the causative agent or disease is not determined and such cases are considered as idiopathic ones.

In order to better characterize patients suffering from EN we have performed a retrospective study analyzing clinical data of subjects hospitalized because of EN. We pay special attention on trigger factors, as well as localization and type of skin lesions. Moreover, we tried to characterize groups of medications used in treatment of EN flares.

## AIM

The aim of our study was to characterize the clinical picture of EN.

## MATERIAL AND METHODS

A total of 44 patients, hospitalized in the Department of Dermatology, Venereology and Allergology in Wrocław were identified and recruited into this study. Data was collected retrospectively based on the medical charts of patients hospitalized because of EN. We have analyzed the data about duration of the disease, the age of the onset of EN and probable trigger factors. Moreover, we have evaluated the type and localization of skin lesions, laboratory abnormalities and medications used in treatment of EN.

All results were analyzed using the software package Statistica® 12.0 (Statsoft, Krakow, Poland). Descriptive statistics included frequencies, median, minimal and maximal values. The significance of the observed differences between groups has been determined by Mann-Whitney U test, and  $\chi^2$  test with Yates correction, if necessary. A p-value lower than 0.05 was considered as statistically significant.

## RESULTS

The female to male ratio was 4.5:1 (36 women and 8 men). The mean age of the patient was  $43.6 \pm 17.7$  years (range: 17-81 years). The mean age of the patients at time of diagnosis was  $43 \pm 17.4$  years old and the mean duration of EN was  $0.6 \pm 1.7$  years.

Almost all patients ( $n = 42$ , 95.5%) presented inflammatory subcutaneous nodules during the course of the disease. Additionally, 45.5% had erythematous-infiltrative lesions and in 8 (18.2%) patients peripheral edemas were observed. Less commonly other types of skin lesions were observed. Clinical presentation of skin lesions described in our patients with EN is summarized in table 1. In all atypical cases the diagnosis was confirmed by histological examination. In addition to skin lesions, 18.2% of patients reported arthralgia, mostly limited to ankle and/or knee joints.

**Tab. 1.** Types of skin lesions observed in patients with erythema nodosum

Type of skin lesions	Number of patients	%
Inflammatory nodules	42	95.5
Erythematous-infiltrative lesions	20	45.5
Peripheral edema	8	18.2
Ulcerations	2	4.5
Papular rash	2	4.5
Wheals	1	2.3
Erythema iris	1	2.3

Regarding the laboratory abnormalities, 52.3% of patients demonstrated raised level of inflammation markers (mainly increased C-reactive protein level and accelerated erythrocyte sedimentation rate) and 25.0% had leukocytosis. No other marked laboratory disturbances were observed. No significant differences were observed between females and males regarding clinical presentation and laboratory abnormalities (data not shown).

Regarding the determined trigger factors, in 50% of patients the onset of the disease was related to a common infectious agent, most commonly to streptococcal pharyngitis which was followed by the appearance of skin lesions typical for EN. Other potential causes of EN were found in 20.5% of patients with only one case of EN triggered by tuberculosis. No underlying cause was stated in 29.5% of patients and these EN cases were considered as idiopathic (fig. 1).

Regarding the treatment of EN almost equally often physicians used systemic corticosteroids, non-steroid anti-inflammatory drugs and antibiotics (56.8 vs. 54.5 vs. 54.5%, respectively). Less than 10% of all patients were treated with azathioprine or dapsone (fig. 2).

## DISCUSSION

Currently, EN is considered as a delayed hypersensitivity reaction to a wide variety of antigens (6). Based on current literature in almost half of cases the etiol-

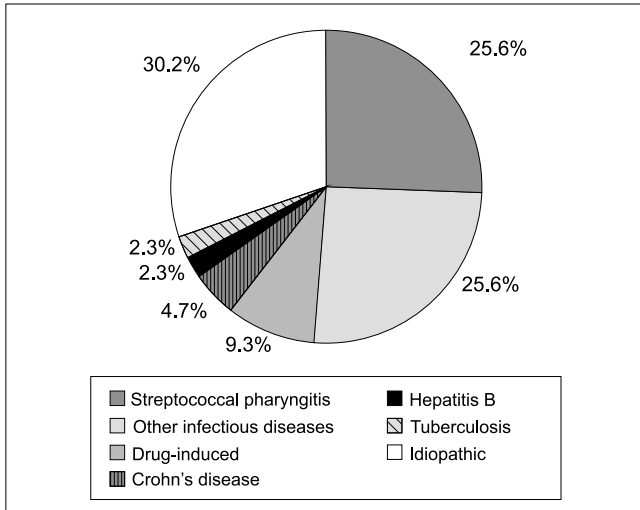


Fig. 1. Trigger factors of erythema nodosum

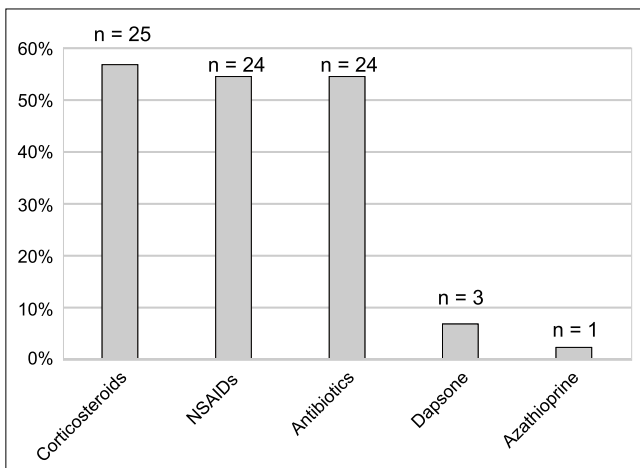


Fig. 2. Treatment of erythema nodosum  
NSAIDs – nonsteroidal anti-inflammatory drugs

ogy of EN remains idiopathic, although there are many potential/probable trigger factors and coexisting conditions. One of the most common cause of EN are bacterial infections. The upper respiratory tract infection by group A beta-hemolytic streptococcal infections account for up to 44% of cases of EN in adults and 48% of cases in children (2-5). The occurrence of EN lesions might also be induced by *Yersinia* spp., mycoplasma, chlamydia, histoplasmosis, coccidioidomycosis and many others (2, 7, 8). Nowadays, tuberculosis, in contrast to the past, is rather infrequent cause of EN in Europe, however, some authors postulate that all patient should be stratified by risk of tuberculosis exposure by performing tuberculin skin test, chest radiography or acid-fast bacilli sputum analysis (2, 4). Along with decreased number of tuberculosis and acute upper respi-

ratory tract infections induced by group A beta-hemolytic streptococcal infections, sarcoidosis develop into more common EN trigger factor. In recently published study by García-Porrúa et al. about one fifth of all EN cases were connected with sarcoidosis (1, 9). This is in contrast to our findings, as we did not observe any case of sarcoidosis in our patient sample, probable due to rather small number of analyzed patients, however, it seems that sarcoidosis is not so common cause of EN as suggested by these authors. However, despite sarcoidosis still should be considered as one of the most common systemic disease triggering EN, physicians should also recognize some other systemic disorders that coexist with EN. In adults, EN often accompanies enteropathies, more frequently ulcerative colitis, than Crohn's disease (4, 10, 11). Interestingly, EN might also be a sign of internal malignancy. Appearance of typical EN skin lesions was observed among patients with acute myelogenous leukemia, Hodgkin's disease, carcinoid tumors and metastatic pancreatic carcinoma (12-15). Moreover, EN presence is observed in up to 4.6% pregnant women, as a result of hormonal disturbances (2).

Drugs are another well-known trigger factor of EN and it is suggested that up to 10% of all EN cases are connected with hypersensitivity reactions to medications. The list of the most common medicines inducing acute flares of EN consist of more than 80 drugs (4). The majority of EN cases has been linked to antibiotics, mostly sulfonamides and amoxicillin, along with contraceptive pills (9, 16, 17). However, it must be underlined, that in patients who developed EN in the course on an infection treated with antibiotics, it could be very difficult to evaluate, whether skin disease was triggered by the drug or the infectious agent itself (4). Nevertheless, in all cases of suspected drug-induced EN, the accused medication should be stopped (2).

## CONCLUSIONS

In conclusion, EN is one of the most common form of panniculitis, however, many aspects of its pathology still remains unanswered. Despite it is believed to be a reactive disease, in many cases the disease is considered idiopathic. The treatment of the disease is mainly based on anti-infectious agents and systemic steroids and non-steroidal anti-inflammatory drugs, however, the randomized controlled studies confirming their efficacy are lacking. Therefore, further studies on EN are urgently needed to better characterize its pathomechanism and to optimize the treatment of affected patients.

## BIBLIOGRAPHY

- Manaa J, Marcoval J: Erythema nodosum. Clin Dermatol 2007; 25: 288-294.
- Schwartz RA, Nervi SJ: Erythema nodosum: a sign of systemic disease. Am Fam Phys 2007; 75: 695-700.
- Mert A, Ozaras R, Tabak F et al.: Erythema nodosum: an experience of 10 years. Scand J Infect Dis 2004; 36: 424-427.
- Requena L, Yus ES: Panniculitis. Part I. Mostly septal panniculitis. J Am Acad Dermatol 2001; 45: 163-183.

5. Kakourou T, Drosatou P, Psychou F et al.: Erythema nodosum in children: a prospective study. *J Am Acad Dermatol* 2001; 44: 17-21.
6. Nguyen GC, Torres EA, Regueiro M, Bromfield G: Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. *Am J Gastroenterol* 2006; 101: 1012-1023.
7. Baldock NE, Catterall MD: Erythema nodosum from *Yersinia enterocolitica*. *Br J Dermatol* 1975; 93: 719-720.
8. Body BA: Cutaneous manifestations of systemic mycoses. *Dermatol Clin* 1996; 14: 125-135.
9. García-Porrúa C, González-Gay MA, Vázquez-Caruncho M et al.: Erythema nodosum. Etiologic and predictive factors in a defined population. *Arthritis Rheum* 2000; 43: 584-592.
10. Sams WM, Winkelmann RK: The association of erythema nodosum with ulcerative colitis. *South Med J* 1968; 61: 676-679.
11. McCallum DI, Kinmont PDC: Dermatological manifestations of Crohn's disease. *Br J Dermatol* 1968; 80: 1-8.
12. Sullivan R, Clowers-Webb H, Davis MD: Erythema nodosum: a presenting sign of acute myelogenous leukemia. *Cutis* 2005; 76: 114-116.
13. Bonci A, Di Lernia V, Merli F, Lo Scocco G: Erythema nodosum and Hodgkin's disease. *Clin Exp Dermatol* 2001; 26: 408-411.
14. Lin JT, Chen PM, Huang DF et al.: Erythema nodosum associated with carcinoid tumour. *Clin Exp Dermatol* 2004; 29: 426-427.
15. Durden FM, Variyam E, Chren MM: Fat necrosis with features of erythema nodosum in a patient with metastatic pancreatic carcinoma. *Int J Dermatol* 1996; 35: 39-41.
16. Beurey J, Jeandidier P, Bermont A: Les complications dermatologiques des traitements antidiabétiques. *Ann Dermatol Syphiligr* 1966; 93: 13-42.
17. Salvatore MA, Lynch PJ: Erythema nodosum, estrogens, and pregnancy. *Arch Dermatol* 1980; 116: 557-558.

received/otrzymano: 6.02.2018  
accepted/zaakceptowano: 27.02.2018