

# Clinical Characteristics of Patients with Erythema Nodosum and Risk of Relapse – a 17-Year Study

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## ABSTRACT

*Erythema nodosum (EN) is the most common type of septal panniculitis which causes inflammation of the subcutaneous fat, being the result of a hypersensitivity reaction to specific triggers. It usually presents with erythematous painful rounded lumps symmetrically on the anterior surface of the lower limbs. Rarely, it may occur in other areas such as thighs, neck and arms. This is a retrospective study describing a cohort of patients hospitalized in the University Hospital of Heraklion, Heraklion, Greece. The present research compares characteristics between patients with and without relapse and identifies independent factors associated with relapse. All patients with EN hospitalized during a 17-year period were included. Data regarding epidemiology, current or recent infections, symptoms, laboratory values and relapses were all recorded and evaluated. In total, 138 patients, of which 27 (19.6%) males, with a median age of 46.5 years, were evaluated. Clinical presentation involved multiple lesions in 115 (83.3%) patients, while 12 (8.7%) of them were febrile. Relapse was noted in 27 (19.6%) subjects. Multivariate logistic regression analysis showed that male gender was associated with a higher risk of relapse, while cases with multiple lesions were associated with a lower risk.*

**Keywords:** erythema nodosum, relapse, septal panniculitis, dermatology.

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## INTRODUCTION

**E**rythema nodosum (EN) is the most common type of septal panniculitis, causing inflammation of the subcutaneous fat. It is the result of a hypersensitivity reaction after exposure to specific triggers and the most common cause of inflammatory nodules (1, 2). Erythema nodosum generally presents with erythematous painful rounded lumps that are usually up to six centimeters in diameter. It is commonly located symmetrically on the anterior surface of the lower limbs; however, in some cases EN may present with lesions in other areas such as thighs, neck and arms. These skin lesions usually resolve spontaneously within one to six weeks without leaving scars (3).

Etiology includes several infections caused by bacteria (such as streptococcal disease), viruses such as Epstein-Barr virus (EBV) or human immunodeficiency virus (HIV), fungi, and parasites as well as systemic diseases (sarcoidosis or inflammatory bowel disease), medications (antimicrobials or contraceptives), malignancies (lymphomas or solid tumors) and pregnancy, while in many cases it is idiopathic (3).

Even though relapsing, in most cases EN may be associated with an infection or medication and could pose a clinical challenge for physicians if an underlying cause is not identified (4). The aim of this retrospective study was to describe a cohort of patients hospitalized in a tertiary hospital due to EN, to compare characteristics between those with and without relapse, and to identify independent factors associated with relapse. □

## METHODS

### Study population

All patients hospitalized in the University Hospital of Heraklion, Crete, Greece, during a 17-year period due to EN were prospectively recorded and retrospectively evaluated. All adult patients with EN diagnosis, based on clinical and histopathological criteria, were included in the present study. Patients were excluded if histopathology did not confirm the clinical diagnosis. Data regarding age, gender, duration of hospitalization, site and number of EN lesions, recent administration of antimicrobials or corticosteroids, laboratory values, and concomitant or recent in-

fections were recorded and evaluated. Relapse was also recorded for up to a year after hospitalization.

The study was approved by the Ethics Committee of the University Hospital of Heraklion, Greece.

### Statistics

Categorical data were analyzed with Fisher's exact test. Continuous variables were compared using Student's t-test for normally distributed variables and Mann-Whitney U-test for non-normally distributed variables. All tests were two-tailed and p-values <0.05 were considered to be significant. Data are presented as numbers (%) for categorical variables and medians [interquartile range (IQR)] or means [ $\pm$ standard deviation (SD)] for continuous variables. A linear regression analysis model was developed to evaluate the effect of several parameters [age, gender, previous steroid use, positive tuberculin (Mantoux) test, bilateral or multiple lesions, fever, previous or concomitant infections, laboratory parameters such as white blood cells and subtypes, erythrocyte sedimentation rate, platelets, C-reactive protein, creatinine, urea, albumin, creatine phosphokinase, lactate dehydrogenase, transaminases, gamma-glutamyl transpeptidase, alkaline phosphatase, prior antimicrobial or non-steroidal anti-inflammatory drug use or previous EN with disease relapse. All were calculated with GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA). A multivariate logistic regression analysis model was developed to evaluate the association of factors identified in the univariate analysis with a p<0.05 with relapse. Multivariate analysis was performed using the SPSS version 23.0 (IBM Corp., Armonk, N.Y., USA). □

## RESULTS

**I**n total, 138 patients with EN were recorded and evaluated during the study period. Table 1 shows subjects' characteristics. The median age of participants was 46.5 years and 27 (19.6%) of them were males. For 40 (29%) patients this was not their first EN episode. A new relapse was noted in 27 (19.6%) patients within one year. Conditions associated with EN occurrence included lower respiratory tract infection in 19 (13.8%) subjects [tuberculosis in two (1.4%)], vi-

TABLE 1. Patients' characteristics

	All patients (n=138)	No relapse (n=111)	Relapse (n=27)	p-value
Age, median (IQR)	46.5 (29-59.3)	47 (26.8-59)	46 (37.8-60.8)	0.3928
Male, n (%)	27 (19.6)	16 (14.4)	11 (40.7)	0.0094
Previous episode, n (%)	40 (29)	29 (26.1)	11 (40.7)	0.1579
Immunosuppression, n (%)	14 (10.1)	11 (9.9)	3 (11.1)	1
Prior antimicrobial treatment*, n (%)	69 (50)	50 (45)	19 (70.4)	0.0306
Positive tuberculin test, n (%)	26 (31.3)	16 (22.5)	10 (83.3)	0.0121
Tuberculosis, n (%)	2 (1.4)	1 (0.9)	1 (3.7)	0.3542
Sarcoidosis, n (%)	4 (2.9)	3 (2.7)	1 (3.7)	1
Pregnancy, n (%)	3 (2.2)	3 (2.7)	0 (0)	1
Bilateral lesions, n (%)	96 (69.6)	79 (71.2)	17 (63)	0.485
Multiple lesions, n (%)	115 (83.3)	96 (86.5)	19 (70.4)	0.2211
Febrile patients, n (%)	12 (8.7)	12 (10.8)	0 (0)	0.1252
WBCs ( $\mu$ L), median (IQR)	7,500 (6,075-9,600)	7,500 (6,200-9,600)	7,320 (5,700-9,100)	0.3103
Neutrophils ( $\mu$ L), median (IQR)	4,650 (3,600-6,000)	4,700 (3,800-6,300)	4,300 (3,100-5,500)	0.2780
ESR (mm at first hour), median (IQR)	32.5 (18.8-49)	33 (19.5-65.5)	28 (17.5-42.5)	0.2101
CRP (mg/dL), median (IQR)	0.76 (0.5-2.2)	0.76 (0.5-2.2)	0.79 (0.44-3.6)	0.9548
Urea (mg/dL), mean (SD)	32 (9.7)	31.1 (9.8)	35.6 (8.2)	0.0308
Creatinine (mg/dL), mean (SD)	0.86 (0.22)	0.85 (0.21)	0.91 (0.23)	0.241
Treatment with steroids, n (%)	32 (23.2)	27 (24.3)	5 (18.5)	0.6181
Duration of stay in hospital, days, median (IQR)	34 (21-49.5)	38 (23-49)	31.5 (19-50)	0.278

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; IQR=interquartile range;

SD=standard deviation; WBCs=white blood cells

\*In the last month

ral infection in 16 (11.6%) [herpes virus simplex (HSV) infection in four (2.9%) and infectious mononucleosis in two (1.4%)], upper respiratory tract infection in 15 (10.9%), skin and soft tissue infection in five (3.6%), sarcoidosis in four (2.9%), pregnancy in three (2.2%), and gastroenteritis and urinary tract infection in two (1.4%) each. Diagnosis of idiopathic EN was reported in 72 (52.2%) patients. In terms of clinical presentation, only 12 (8.7%) patients developed fever, while 115 (83.3%) had multiple skin lesions and in 96 (69.6%) lesions were bilateral. Inflammatory parameters were relatively low, with median

C-reactive protein (CRP) being 0.76 mg/dL, and median erythrocyte sedimentation rate 32.5 mm at first hour. Steroids were used for treatment in 32 (23.2%) patients.

Comparison of characteristics between patients with and without relapse revealed that relapsing ones were more likely to be male, had a positive tuberculin test, higher laboratory value of urea and were more likely to have had an antimicrobial treatment during the last month, all in a statistically significant way. The follow-up period was at least a year. A univariate regression analysis showed that gender, positive tuberculin

TABLE 2. Logistic regression analysis regarding relapse

	Univariate analysis p-value	Multivariate analysis p-value	OR (95% CI)
Male gender	0.0018	0.038	3.969 (1.077-14.621)
Positive tuberculin test (Mantoux)	0.0075	0.494	1.549 (0.442-5.425)
Multiple lesions	0.0442	0.024	0.23 (0.064-0.824)
Urea (per mg/dL)	0.0308	0.468	1.023 (0.962-1.089)
Prior antimicrobial treatment	0.0181	0.48	1.47 (0.505-4.276)

test, limited number of lesions, higher urea value and recent antimicrobial treatment during the last month were all associated with relapse. However, a multivariate logistic regression analysis identified only male gender to be independently positively associated with relapse and presentation of multiple lesions independently negatively associated with relapse. All patients were Caucasians of Greek origin. The results of the regression analysis are shown in Table 2. □

## DISCUSSION

The present study described a cohort of patients with EN hospitalized in a University Center and evaluated the likelihood of disease relapse. The study findings showed that male gender and EN presentation without multiple lesions were independently associated with higher likelihood of relapse.

The etiology of EN varies and it is highly dependent on the geographic latitude and patients' race. The most common causes are infections in up to 50% of patients, followed by sarcoidosis (25%), drugs (10%), pregnancy (5%) and enteropathies (5%) (2). However, in many cases the cause remains unknown and is therefore termed idiopathic (2, 5, 6). The disease causes inflammation of the subcutaneous fat, leading to erythematous painful rounded lumps, most commonly at the lower extremities that are often bilateral and symmetrical and are usually up to six centimeters in diameter.

Recurrent EN can pose diagnostic and therapeutic dilemmas, since it may be associated with several conditions that may not be evident at the time of the first diagnosis (7-12). About 20% of

our subjects had a relapse during the follow-up period. Male gender was discovered to be independently associated with relapse, while the presence of multiple lesions was found to be negatively associated with relapse. Interestingly, no studies in the literature are specifically focusing on relapsing EN so far; thus, the present one is the first to assess factors associated with relapses.

In our cohort there was a female predominance, which was in line with the literature, since EN was found to occur up to five times more often in women (13, 14). Patients' median age was 47 years, which was higher than that reported in other studies, which describes the peak between 18 and 34 years (13-16). Interestingly, multiple and bilateral lesions were noted in 83% and 70% of participants to our study, respectively, while in the literature bilateral lesions were noted in almost all patients (13). Furthermore, inflammatory parameters such as erythrocyte sedimentation rate and white blood count, which were observed in the present population, had lower values than those reported by other studies (13). This observation correlates with the much lower proportion of patients who had fever in the EN cohort of our study. Indeed, only 9% of our subjects developed temperature higher than 38°C, while in other studies the proportion of febrile patients reached 40% (13).

Fifty-five percent of our patients were considered to have idiopathic EN, a proportion similar to that in the literature, while most identified causes had infectious origin. It is of note that streptococcal diseases were much less frequent as compared to other studies that had described

them as the most common underlying cause (13).

The present study has some limitations that should be noted, including the relatively small sample size, and the fact that it was performed in a single center, which may limit the generalization of results. □

### CONCLUSION

The present study has shown that infections were the most common cause of EN, with a

trend towards less streptococcal infections, while most cases remain idiopathic. Relapsing is associated with male gender, while multiple lesions are associated with less chances of relapse. □

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