

Clinical, Epidemiological, and Etiological Changes in Erythema Nodosum

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ABSTRACT: **Background:** Erythema nodosum (EN) is the most common type of panniculitis, commonly secondary to infectious diseases.

Objectives: To elucidate the causative factors and the clinical presentation of patients with EN (2004–2014) and to compare their data to those reported in a previous study.

Methods: A retrospective study was conducted of all patients diagnosed with EN who were hospitalized at Soroka University Medical Center (2004–2014). The clinical, demographic, and laboratory characteristics of the patients were compared to those in a cohort of patients diagnosed with EN from 1973–1982.

Results: The study comprised 45 patients with a diagnosis of EN. The most common symptoms of patients hospitalized with EN were arthritis or arthralgia (27% of patients). Patients with EN, compared to those reported in 1987, has significantly lower rates of fever (18% vs. 62% $P < 0.001$), streptococcal infection (16% vs. 44%, $P = 0.003$), and joint involvement (27% vs. 66%, $P < 0.001$). In addition, fewer patients had idiopathic causes of EN (9% vs. 32%, $P = 0.006$).

Conclusions: In the past decades, clinical, epidemiological, and etiological changes have occurred in EN patients. The lowering in rate of fever, streptococcal infection, and joint involvement in patients with EN are probably explained by improvements in socioeconomic conditions. The significantly decreasing rate of idiopathic causes of EN is possibly due to the greater diagnostic accuracy of modern medicine. The results of the present study demonstrate the impact of improvements in socioeconomic conditions and access to healthcare on disease presentation.

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and the presence of radial granulomas [1]. It is presumed that EN occurs as a result of a delayed hypersensitivity reaction to antigens. The accompanying symptoms in EN include weight loss, malaise, low grade fever, cough, arthralgia, and arthritis [1].

Infectious diseases, mainly streptococcal pharyngitis, have been associated with the development of EN. But, EN may be the presenting sign of sarcoidosis, inflammatory bowel disease (IBD), or other systemic inflammatory and malignant diseases [1-5]. This finding is explained by the immune pathophysiological pathways of EN [6]. There is a high incidence of EN during pregnancy, as well as during oral contraception usage [1,7,8]. In several cases EN develops in the absence of an underlying disease [1,7].

The prevalence of EN is 1 to 5 cases per 100,000 individuals [2,9]. In adults, it is more common among women, with a male-to-female ratio of 1:6. Peak incidence occurs in individuals between the ages of 15 and 40, although EN can occur in any age group [2,9].

Erez and colleagues [10] reported the clinical features and possible etiological causes of 50 patients diagnosed with EN from 1973 to 1982 in the southern district of Israel [10].

The purpose of our study was to describe the causative factors and the clinical picture of patients diagnosed with EN from 2004 to 2014, in the southern district of Israel, and to compare it to the data from the 1980s [10].

PATIENTS AND METHODS

STUDY POPULATION

The Soroka University Medical Center, a tertiary medical center located in the southern district of Israel, serves more than one million people annually. The study population included all patients aged 18 years or older who were hospitalized with possible diagnosis of EN (ICD-9 code 695.2, 017.1) from 2004 to 2014. Their electronic health records were retrieved.

In the first screen, 224 cases with EN ICD-9 codes were identified. Inclusion criteria were histology of panniculitis, if applicable, or clear clinical diagnosis of EN made by internal medicine physician, rheumatologist, or dermatologist [1,11]. Two independent internal medicine physicians reviewed each

Erythema nodosum (EN) is a clinical entity usually characterized by the development of deep, painful, and erythematous nodules over the anterior aspect of both legs. The histological hallmarks of the disease include panniculitis of the subcutaneous fat tissue of the skin, the presence of inflammatory cells in the septa between subcutaneous fat lobules, lack vasculitis,

medical record, excluding cases without histological or clear clinical evidence of EN or in cases with significant missing data. In a situation of disagreement, both physicians discussed each case separately to reach a consensus. Of the 224 patients, 45 patients fulfilled inclusion criteria and were included in the study (19 with diagnostic histology and the others according to clinical diagnosis). Clinical, laboratory, and demographic characteristics were obtained from the medical informatics system.

The diagnosis of streptococcal infection was defined as a combination of clinical pharyngitis and positive throat culture or positive anti-streptolysin O antibody (ASLO) with a titer above 300 units [12,13].

The clinical, demographic, and laboratory characteristics of the patients were compared to those reported in a cohort of patients with EN that was published in 1987 [10]. We created a unified dataset that included both cohorts based on our sample and the previous one. The comparison was made after receiving permission from the authors.

STATISTICAL ANALYSIS

No formal power calculation was performed because all cases in the defined period were analyzed if they met the inclusion criteria. Categorical data are expressed as absolute numbers and percentages. Continuous parameters are presented as mean ± standard deviation. Differences between the two cohorts were assessed with the independent-sample *t*-test for continuous variables and chi-square test ($\times 2$) for categorical variables. Because we did not have the original data from 1987, we could only use the published material. Hence, we could perform univariate analysis, but not multivariate. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Two-sided *P* values < 0.05 were considered statistically significant.

Institutional review board approval was obtained prior to initiation of this study.

RESULTS

The study was comprised of 45 patients with a diagnosis of EN. Of these patients, 87% were women with a mean age at diagnosis of 35 years (35.2 ± 15); 84% were admitted with their first episode of EN, and 16% were diagnosed with recurrent EN.

The most common symptoms of patients hospitalized with EN were arthritis or arthralgia (27% of patients) and fever (18% of patients).

Evidence for streptococcal infection with a positive throat culture or elevated serological test for ASLO above 300 U/ml were obtained in seven patients from our cohort.

The most common suspected etiology of EN in our population was streptococcal pharyngitis (16%). Other possible etiologies were oral contraceptive use (13%), idiopathic (9%), sarcoidosis (7%), IBD (7%), viral hepatitis (7%), and vasculitis (4%).

Table 1. Baseline and clinical characteristics of patients diagnosed with erythema nodosum in the 1980s vs. the 2004–2014

| | 1980s (n=50) | 2004–2014 (n=45) | P value |
|-----------------------------------|-------------------------|------------------|---------|
| Females, n (%) | 44 (88) | 39 (87) | 0.845 |
| Age 14–45 years, n (%) | 41 (82) | 35 (78) | 0.607 |
| Fever*, n (%) | 31 (62) | 8 (18) | < 0.001 |
| Joint involvement, n (%) | 33 (66) | 12 (27) | < 0.001 |
| Positive CRP (> 5 mg/l), n (%) | 18 (50) | 12 (52) | 0.871 |
| Streptococcal infection, n (%) | Total** | 7 (16) | 0.003 |
| | Positive ASLO (> 1:300) | 7 (16) | 0.751 |
| | Positive culture | 0 (0) | 1.000 |
| Pregnancy, n (%) | 3 (6) | 1 (2) | 0.619 |
| Medications, n (%) | 3 (6) | 2 (4) | 1.000 |
| Contraceptive, n (%) | 2 (4) | 6 (13) | 0.144 |
| Sarcoidosis, n (%) | 1 (2) | 3 (7) | 0.342 |
| Tuberculosis, n (%) | 1 (2) | 0 (0) | 1.000 |
| Inflammatory bowel disease, n (%) | 1 (2) | 3 (7) | 0.342 |
| T-cell immunodeficiency, n (%) | 1 (0) | 0 (0) | 1.000 |
| Vasculitis, n (%) | 0 (0) | 2 (4) | 1.000 |
| Viral hepatitis, n (%) | 0 (0) | 3 (7) | 1.000 |
| Malignancy, n (%) | 0 (0) | 1 (2) | 1.000 |
| Idiopathic, n (%) | 16 (32) | 4 (9) | 0.006 |

*Defined as admission diagnosis

**Defined as clinical pharyngitis, positive throat culture or positive ASLO > 1:300 [14,17]
ASLO = anti-streptolysin O, CRP = C-reactive protein

Table 1 compares the characteristics of the patients with EN included in this study with those reported in the 1980 article [10]. The data indicate that patients with EN in the last decade have significantly lower rates of fever (18% vs. 62%, *P* < 0.001), streptococcal infection (16% vs. 44%, *P* = 0.003), and joint involvement (27% vs. 66%, *P* < 0.001) compared to those reported in 1987. In addition, fewer patients had idiopathic disease (9% vs. 32%, *P* = 0.006). No patients with tuberculosis were found in the latter cohort.

DISCUSSION

The epidemiology of EN is diverse in different geographic regions. This diversity is expressed in prevalence and etiological cause.

A higher incidence (12–14 cases /100,000 person-years) of EN was reported in Scandinavia. In a study conducted in Finland, Hannuksela found sarcoidosis to be the major cause of EN [14]. In a report from Egypt, 40% of cases of EN were diagnosed among patients with streptococcal disease [15].

In the past, tuberculosis was the major disease associated with EN, but in the last decades this etiology was rare, especially in developed countries [11].

In a retrospective study of 24 children with a diagnosis of EN in Israel, most cases were associated with non-mycobacterial infections, mainly streptococcal infection and Epstein–Barr virus, or with non-infectious inflammatory conditions, especially IBD. Tuberculosis was not noted [16].

Erez and colleagues [10], in the first epidemiological study of EN in Israel, reported the etiological causes of EN. The most commonly associated disease was streptococcal pharyngitis, which occurred in 44% of the cases. There was only one case of EN associated with tuberculosis.

From 2004–2014, as compared to the 1980s, streptococcal infection as an etiological cause of EN decreased significantly. The reason is probably due to the widespread use of antibiotics in the early treatment of streptococcal infection, especially in Western countries [17].

The decreasing number of patients with EN and fever is probably also due to decreased streptococcal infection as an etiologic factor of EN.

An additional explanation of this trend may be that in the last decades there has been an improvement in the socioeconomic level in Israel. Israel is a developed country and a member of the OECD. Medical services in Israel are also recognized as Western and modern.

This modernization and changing lifestyle in Israel, in particular in the southern region that in the past was considered to be rural and with poor medical services, can cause changes in disease characteristics. For these same reasons, tuberculosis is not an noted cause of EN in southern Israel.

Significantly fewer cases of idiopathic causes of EN, possibly due to greater diagnostic accuracy of modern medicine, are also found. There is also a tendency toward an increase in EN that is secondary to oral contraceptive use, IBD, sarcoidosis, and other vasculitis, which is also possibly due to the improved diagnostic accuracy of modern medicine.

The limitations of the present study are primarily because it was a retrospective study conducted at a single institution; however, this limitation strengthens the comparative data obtained.

Further research is needed to assess the impact of these trends on the prevalence and morbidity of EN in southern Israel and to determine whether these patterns are reflected in other populations, particularly in countries that have witnessed an improvement in socioeconomic conditions.

CONCLUSIONS

In the past decades, clinical, epidemiological, and etiological changes have occurred in EN patients. The lowering in rate of fever, streptococcal infection, and joint involvement in patients

with EN are probably due to improvements in socioeconomic conditions. The significantly decreasing rate of idiopathic causes of EN is possibly because of the greater diagnostic accuracy of modern medicine. The results of the present study demonstrate the impact of improvements in socioeconomic conditions and access to healthcare on disease presentation. Further research is needed to study this impact on other diseases and in other regions of the world.

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“Associate with men of good quality if you esteem your own reputation; for it is better to be alone than in bad company”

George Washington, (1732–1799), first president of the United States