Erythema nodosum in children: evaluation of 39 patients

Türkan Aydın-Teke, Gönül Tanır, Gülsüm İclal Bayhan, Özge Metin, Nur Öz

Division of Pediatric Infectious Diseases, Dr. Sami Ulus Maternity and Children's Training and Research Hospital, Ankara, Turkey. E-mail: turkanteke@gmail.com

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Erythema nodosum (EN) has been associated with various infectious and noninfectious diseases. A total of 39 EN patients seen between May 2005 and February 2012 were evaluated retrospectively in this study. The etiology of EN was established in 22 of the 39 children (56.4%). Streptococcal infection was the most common cause (23%), followed by tularemia (10.2%) and tuberculosis (latent tuberculosis infection (LTBI) 5%, pulmonary tuberculosis 2.5%). Miscellaneous conditions were as follows: Behçet disease (2.5%), cytomegalovirus (CMV) (2.5%), *Giardia lamblia* infection (2.5%), and sarcoidosis (2.5%). Four cases had double diagnoses as follows: streptococcal infection plus *Mycoplasma pneumoniae*, streptococcal infection plus LTBI, streptococcal infection plus *Chlamydophila pneumoniae*, and tularemia plus LTBI. Streptococcal infections are the most common causative factors of EN among children in our setting. In some cases, either of two diagnoses may induce EN. Etiologic factors should be investigated for the diagnosis and specific treatment of the underlying diseases.

Key words: erythema nodosum, evaluation, etiology, children.

Erythema nodosum (EN) is a cutaneous reaction pattern characterized clinically by the presence of erythematous tender nodules and raised plaques located predominantly over the extensor aspects of the legs and histologically by a septal panniculitis. The diagnosis of EN is usually clinical. EN has been associated with various infectious and noninfectious diseases. In addition, various pharmacological agents are also considered responsible for EN. The purpose of this retrospective study was to evaluate the epidemiology, etiology and clinical manifestations of EN among children.

Material and Methods

We retrospectively reviewed 39 patients with EN who attended the Department of Pediatric Infectious Diseases at Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital between May 2005 and February 2012. The diagnosis of EN was based on the presence of tender erythematous nodules and plaques on the lower extremities that lasted for several days without suppuration or ulceration. We collected the following data from past medical records: gender, age, drug usage, preceding and concurrent systemic symptoms, physical examination findings, duration, distribution (bilateral or unilateral) and location of the lesions, laboratory investigations, histopathological findings, and applied treatment(s). EN recurrence was defined as the re-emergence of the typical erythematous nodules after a disease-free period of at least one month. Laboratory investigations included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tuberculin skin test (TST), throat culture, antistreptolysin O titer (ASO), chest X-ray, and stool examination for parasites. Anti-nuclear antibody (ANA), and anti-double stranded DNA (anti-dsDNA) levels were determined if required. The diagnosis of past or present streptococcal infection was established using at least one of two criteria: a high level of ASO (>400 UI/ml) or the presence of *Streptococcus pyogenes* in the throat. Patients with compatible signs or symptoms, positive TST, history of contact with an adult index case, and radiological findings were diagnosed as pulmonary tuberculosis. Patients with only positive TST or QuantiFERON-TB Gold test but with no symptoms or radiological findings were defined as latent tuberculosis infection

(LTBI). Enzyme-linked immunoassay (ELISA) tests for *Mycoplasma pneumoniae, Chlamydophila pneumonia*e, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) were performed, and positivity for EBV, *M. pneumoniae* and *C. pneumonia*e was accepted as diagnostic for these infections. Serum and urine polymerase chain reaction (PCR) was also used to confirm CMV infection. Tularemia was considered in the presence of compatible clinical signs, and diagnosis was confirmed with a serum microagglutination test of ≥1/160 titer. Ophthalmologic examination and skin biopsy findings were recorded if available. The diagnosis of sarcoidosis was established by the histopathological examination of skin biopsy material. Behçet disease was diagnosed according to the diagnostic criteria established by the International Study Group for Behçet disease[1].

Statistical Analysis

Data were entered into a database, and statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v15.0). The significance of differences between groups was evaluated using Mann-Whitney U test. $P<0.05$ was accepted to indicate statistical significance.

Results

A total of 39 cases of EN identified over the seven-year period were enrolled in the study (21 females, 54%; 18 males, 46%). The mean age was 11.3±3.6 years (range: 4-18 years), 11.4±3.9 years in boys and 11.1±3.3 years in girls ($p>0.05$). Four (10%) patients were aged 0-6 years, 24 (62%) 7-12 years and 11 (28%) 13-18 years. The most common clinical findings were fever and sore throat (in 14 children, 35.8%). The lesions were bilateral in 36 (92%) patients and located on lower extremities in 38 (98%) patients, and in 4 of them, the lesions were located on the upper as well as lower extremities. The mean duration of the nodules before admission was 6.6±4.6 days (range: 1-20 days). The nodules recurred in 13 (33.3%) of the patients prior to admission. Patient age, EN localization and presence of recurrence according to the coexistent diseases are demonstrated in Table I. The mean total leukocyte count was 10,280/mm^3 (range: 6000-23,000/mm^3), and it was higher than 10,000/mm^3 in 16 patients (41%). The mean CRP level of the study group was 42.1 mg/L (range: 1-231 mg/L), and it was higher than 8 mg/L in 24 patients (68.5%). The mean ESR of the study group was 47.1 mm/h (range: 4-120 mm/h), and it was higher than 20 mm/h in 23 patients (60%). The total leukocyte count, CRP and ESR levels according to the coexistent diseases are shown in Table II. None of the patients had been exposed to drugs such as antiepileptic agents, sulfonamides or oral contraceptives. Skin biopsies were performed in three patients and EN was confirmed. An eight-year-old boy with EN had cutaneous lesions (pinkish papules with yellow highlights) on his face and no systemic findings. Biopsy from the cutaneous lesions on the face revealed non-caseating granulomas. The biopsy from the nodules on the leg demonstrated EN. The etiologic factor could not be identified in 17 (43.6%) children.

All the EN patients in this study were managed with bed restriction and non-steroidal anti-inflammatory drugs in addition to the specific treatment of the coexistent disease.

Discussion

It has been demonstrated that EN occurs three to six times more frequently in women than men, although the sex ratio is approximately equal before puberty[2]. In our series, the ratio was similar, but in contrast to previous studies, we did not observe a female predominance after 12 years of age. This was likely related to the fact that etiologic factors in our series were primarily infectious diseases and not dependent on gender. It has been reported that EN occurs between the second and fourth decades of life, with the peak incidence between 20 and 30 years of age, probably because of the high incidence of sarcoidosis at this age[3]. The mean age of EN in childhood is reported as approximately 8-10 years[4,5]. In our study, the mean age of the patients was 11 years in both genders, and most of the cases were aged 7-12 years, probably because of the more frequent incidence of streptococcal infections in this age group. EN is unusual before the age of two years, and in our study, the youngest child was four years old.

The diagnosis of EN can usually be made clinically, with no need for histopathological examination for the diagnosis[6]. With the

exception of three cases, all our patients were diagnosed with EN based upon clinical findings.

It has been reported that in EN cases, acute phase reactants generally increase. In this respect, our results were similar to those reported in the literature[4,7].

The legs were the most common sites of involvement and although usually bilateral, lesions can also be unilateral. In this study, four (10.2%) patients had EN located on the upper as well as lower extremities.

Erythema nodosum (EN) has been associated with a variety of infectious diseases, most notably tuberculosis, streptococcal infections, *Yersinia enterocolitica, Y. pseudotuberculosis,* cat-scratch disease, tularemia, acute upper respiratory tract infections, Q fever, and epidemiologic internal organ mycoses (histoplasmosis, coccidiomycosis). Chronic inflammations including Behçet disease, Reiter disease, systemic lupus erythematosus, inflammatory bowel disease, and sarcoidosis, malignant diseases, and exposure to certain medications can be involved in the etiology of EN. Streptococcal infection was reported as the most common cause of EN in the pediatric as well as adult population[3]. Our data confirm the predominance of streptococcal infections among children with EN.

The second most common etiologic factors in our study were tularemia and tuberculosis. It was reported that 13 of 98 patients had EN during two tularemia outbreaks in Turkey in

Table I. Patient Age, Location of the Lesions and Presence of Recurrence in Patients with EN According to the Etiological Diseases

Etiology	No.	%	Mean age (range)/age (years)	Located on both extremities	Recurrence
Streptococcal infection	9	23	13.7 (10-18)	No	Yes (2/9)
Streptococcal[1] plus *M. pneumoniae* infection	1	2.5	10	No	No
Streptococcal[2] infection plus LTBI	1	2.5	16	Yes	Yes
Streptococcal[2] plus *C. pneumoniae* infection	1	2.5	13	No	No
M. pneumoniae infection	1	2.5	9 (8-10)	No	No
Tularemia	3	7.7	8.3 (6-10)	No	No
Tularemia plus LTBI	1	2.5	10	No	No
Behçet disease	1	2.5	16	No	Yes
CMV infection	1	2.5	12	Yes	No
Pulmonary tuberculosis	1	2.5	11	Yes	No
Giardia lamblia infection	1	2.5	12	No	No
Sarcoidosis	1	2.5	8	No	No
Undetermined*	17	43.5	10.3 (4-18)	Yes (1/16)	Yes (8/16)
Total	39	100	11.3 (4-18)	4	12

*Eight children with upper respiratory tract infection.
[1] Diagnosed with throat culture.
[2] Diagnosed with increased antistreptolysin O (ASO) titer.
C. pneumoniae: Chlamydophila pneumoniae. CMV: Cytomegalovirus. EN: Erythema nodosum. LTBI: Latent tuberculosis infection. *M. pneumoniae*: *Mycoplasma pneumoniae*.

Table II. The Total Leukocyte Count (mean/range), CRP (mean/range) and ESR (mean/range) Levels of the EN Patients According to the Etiological Diseases

Etiology (number of patients)	Leukocyte count (/mm³) (mean/range)	CRP (mg/L) (mean/range)	ESR (mm/hour) (mean/range)
Streptococcal infection[9]	12222 (7000-23000)	73.6 (3-231)	77.5 (4-120)
Streptococcal infection plus *M. pneumoniae*[1]	11000	80	37
Streptococcal infection plus LTBI[1]	11000	5	27
Streptococcal[2] infection plus *C. pneumoniae*[1]	6000	68	42
M. pneumoniae infection[2]	11000	49.5 (19-80)	41 (37-45)
Tularemia[3]	12000 (9000-15000)	40.6 (4-71)	78.3 (70-90)
Tularemia plus LTBI[1]	10000	63	51
Behçet disease[1]	6000	12	20
CMV infection[1]	8000	17	85
Pulmonary tuberculosis[1]	11000	65	65
Giardia lamblia infection[1]	9000	3	11
Sarcoidosis[1]	8000	1	8
Undetermined[17]	9647 (6000-18000)	28.5 (1-168)	29.2 (5-100)

C. pneumoniae: Chlamydophila pneumoniae. CMV: Cytomegalovirus. CRP: C-reactive protein. EN: Erythema nodosum. ESR: Erythrocyte sedimentation rate. LTBI: Latent tuberculosis infection. *M. pneumoniae*: *Mycoplasma pneumoniae*.

1993[8]. Following a recent tularemia outbreak that emerged in Central Anatolia, Turkey in 2009-2010, it was reported that 1 of 39 patients had EN[9]. We think that the cases with tularemia and EN are probably epidemiologically linked to this outbreak. EN is one of the hypersensitivity reactions to tuberculoprotein. EN has been described in children as a manifestation of primary tuberculosis. In our series, EN was related to both active tuberculosis and LTBI. It has been reported that EN can be the first and only presentation of tuberculosis in a patient with/without evidence of active disease[10]. Tuberculosis should be investigated and excluded, especially in endemic areas, as an underlying etiology of EN.

M. pneumoniae infection is one of the most common etiologic agents of respiratory tract infections and community-acquired pneumonia. It is often accompanied by various extrapulmonary complications such as hepatitis, myositis, arthritis, central nervous system involvement, leukocytoclastic vasculitis, and a variety of cutaneous manifestations. EN has been reported among the cutaneous manifestations of *M. pneumoniae* infection[11,12]. In our study, *M. pneumoniae* was diagnosed in two cases with EN and in a third case with EN plus concomitant acute streptococcal infection. Generally, streptococcal infection precedes the onset of EN by approximately three weeks. We thus considered that *M. pneumoniae* infection might have been responsible for EN in that patient. In a series that included 35 children, three cases of *M. pneumoniae* infection were associated with EN[5].

The association of *C. pneumoniae* infection with EN has been reported rarely. One case was a 42-year-old woman in whom EN was caused by ascariasis and *C. pneumoniae* pulmonary infection. The others were 17 and 11 years old and had *C. pneumoniae* infection and EN. Some authors have suggested that *C. pneumonia* (strain TWAR) can elicit EN[13,14]. In our study, one case of *C. pneumoniae* infection associated with EN had been treated for streptococcal infection before the nodules developed. When therapy with a macrolide antibiotic was prescribed, his lesions improved gradually with no recurrence.

The association between *G. lamblia* infection and EN is reported very rarely in the English

literature[15]. In our series, there was one case with EN associated with *G. lamblia* infection. We suggest a possible role of Giardia infection in the pathogenesis of EN.

The development of EN is related to CMV rarely, but has been reported in a previously healthy adult patient with acute CMV mononucleosis and in an adult heart transplant patient as an unusual presentation[16,17]. We diagnosed CMV infection in a 12-year-old boy with EN by serum CMV immunoglobulin (Ig) M positivity in addition to a urine CMV viral load at 4300 copy/ml.

Behçet disease is prevalent in Turkey, with a peak incidence at 20-40 years of age. In a study from Turkey, it was found that the 110 children in the study represented 3.3% of the total number of Behçet patients. That study revealed that 62.7% of pediatric cases were girls and 37.3% were boys[18]. In our study, Behçet disease was observed in a 16-year-old male patient. In a study that included 2,313 Behçet patients, EN was reported in 47.6% of the patients[19].

The skin manifestations of sarcoidosis are classified as specific, where biopsy reveals non-caseating granulomas, and non-specific, typically EN[20]. Our patient with sarcoidosis had the histopathological finding of non-caseating granulomas. It has been reported that 20-35% of patients with systemic sarcoidosis have skin lesions, but cutaneous sarcoidosis can occur without systemic disease. We thought that our patient had cutaneous sarcoidosis with the typical histopathological finding and EN. EN was noted in 31% of sarcoidosis patients in one study[21].

The etiological factor of EN remained undetermined in 41% of cases in the present study. It was reported that approximately 30-50% of pediatric cases are idiopathic[22]. In the present study, EN recurrences were seen mostly in the patients with undetermined cause. In a series that included 100 patients (mean age: 37 years), recurrences were reported in two-thirds of the EN patients. The authors concluded that recurrences are more common in patients with idiopathic EN, as in our study[23]. In another series that included 35 pediatric patients, the etiology of EN remained undetermined in eight of them, and recurrences were reported in only two children[5].

In the present study, patients received symptomatic treatment and mainly non-steroidal anti-inflammatory drugs to alleviate the pain. Although the disorder is usually self-limited, laboratory investigations should be done for a possible underlying cause that may require specific treatment, such as Behçet disease.

Our study has several limitations, including the fact that patients were recruited in a pediatric infectious diseases department of a tertiary referral center, and thus, they may not be completely representative of patients with EN visited in other settings. Moreover, while the number of patients in our study was not low compared to the literature, it was low for giving the prevalence of the various etiologies, and this is a retrospective study, such that the ratio of the cases of EN without a determined cause was high.

In conclusion, streptococcal infections were the most common causative factors of EN among children in our setting, followed by tuberculosis and tularemia. In some cases, either of two diagnoses may induce EN. Etiologic factors should be investigated in EN cases for the diagnosis and specific treatment of underlying diseases, such as LTBI, *M. pneumoniae*, *C. pneumoniae*, tularemia, *G. lamblia* infections, Behçet disease, and sarcoidosis.

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