Erythema nodosum in childhood: evaluation of ten patients

A. Bülent Cengiz, Ateş Kara, Güler Kanra, Gülten Seçmeer, Mehmet Ceyhan
Unit of Infectious Diseases, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Cengiz AB, Kara A, Kanra G, Seçmeer G, Ceyhan M. Erythema nodosum in childhood: evaluation of ten patients. Turk J Pediatr 2006; 48: 38-42.

Erythema nodosum (EN), which is a rare skin manifestation among children, is precipitated by a range of infectious and non-infectious diseases. The purpose of this study was to evaluate the epidemiology, etiology, clinical manifestations and course of EN among children.

A total of 10 patients diagnosed with EN between January 2000 and March 2004 at Hacettepe University İhsan Doğramacı Children's Hospital, Pediatric Infectious Diseases Outpatient Clinic, were studied retrospectively. The study population consisted of five girls and five boys, with a mean age of 8.8±3.3 years (range, 4-14 years). In five of the 10 children (50%), the etiology of EN was established: three had streptococcal infection and two were diagnosed as primary tuberculosis; the etiology of EN could not be determined in 50% of the cases. The duration of the recovery of lesions varied from 4 to 12 days (mean, 8.2±2.6 days).

Our data confirm the predominance of streptococcal infections among the etiologic factors while also considering tuberculosis as a causative factor among children with EN in Turkey.

Key words: childhood, erythema nodosum, streptococcal infection, tuberculosis.

Erythema nodosum (EN), which is a self-limited skin manifestation, is characterized by the development of indurated, red, hot, elevated, tender, ovoid nodules 1-3 cm in diameter[1,2]. Defined histologically as a septal panniculitis[1], EN is precipitated by a range of infectious and non-infectious diseases[1-4]. In addition, various pharmacological agents are also considered responsible for EN[1,4]. The prevalence of EN, which has a rare cutaneous reaction pattern, is estimated to be 2.4 per 10,000 in the general population per year in England[5]. While EN can occur at any age, it most commonly occurs between the ages of 20 and 30 and its incidence is lower among children than among adults[1,3]. The relative frequencies of the causative diseases of EN vary among reports from different countries[1]. The purpose of this study was to evaluate the epidemiology, etiology, clinical manifestations and course of EN in children at Hacettepe University İhsan Doğramacı Children's Hospital in Ankara, Turkey.

Material and Methods

A total of 10 patients diagnosed with EN between January 2000 and March 2004 at Hacettepe University İhsan Doğramacı Children's Hospital, Pediatric Infectious Diseases Outpatient Clinic, were studied retrospectively. For this purpose, the patients' clinical and laboratory records were reviewed. The main clinical criteria considered when including patients diagnosed with EN in this study were tender erythematous nodules or plaques which started in the last three weeks with diameter of 1 cm or more, located bilaterally mainly on the legs, with color changing from red to yellow-brown and ending without any ulceration or scarring in 3-6 weeks[1-3].

In all cases, hemogram, total white blood cell count, leukocyte differential count, erythrocyte sedimentation rate (ESR), anti-streptolysin-O (ASO) level, throat swab for bacteriologic culture, chest roentgenography and tuberculin reactivity were investigated and urinalysis

was performed. Other laboratory tests were performed as necessary. C-reactive protein (CRP) level was measured in six patients. Epstein-Barr virus, hepatitis B virus (HBV) and hepatitis C virus (HCV) serodiagnoses were carried out in four cases, and human immunodeficiency virus (HIV) serodiagnosis was carried out in only one case. Serum antibodies to Mycoplasma pneumoniae were measured in two cases. Salmonella and Brucella agglutination tests were performed in one case. Antinuclear antibodies were studied in three cases and anti-dsDNA antibodies in two cases. Rheumatoid factors were investigated in four cases. Serum immunoglobulin A (IgA), IgM and IgG levels were measured in one case and complement component C3 and C4 in two cases. Liver function tests were performed in five cases. Stool cultures for Yersinia enterocolitica, Campylobacter, Salmonella and Shigella were performed in one case. Amebiasis was investigated in one patient. In cases where tuberculin skin tests were positive, additional investigations were performed, including cultures of sputum or gastric lavage for Mycobacterium tuberculosis, history of exposure to a patient with active pulmonary tuberculous, tuberculin testing of all household members and roentgenological examination of the chest of household members.

The diagnosis of streptococcal infection was established using two criteria: a high level of ASO (above 400 UI/ml) or the presence of Streptococcus pyogenes in the throat[3].

The type and location of skin lesions were identified. If the child had fewer than six lesions on each leg, we considered the number of lesions as low[2]. The histories of all patients were reviewed in detail from their medical records in terms of drug intake (e.g., antiepileptics, especially phenytoin; antibiotics, especially sulfonamides), recent immunization and prodromal and concomitant symptoms of the disease. The cases were evaluated to determine whether they had chronic underlying disease. Symptoms which occurred within the last two weeks before the onset of EN were regarded as prodromal symptoms[2]. Similarly, recent immunization was regarded as vaccination in the last two weeks before the onset.

The statistical analysis was performed using SPSS for Windows Release 7.5 program.

Results

There were 10 children (5 girls, 5 boys) with EN, with mean age of 8.8±3.3 years (range, 4-14 years) (Table I). Four of the patients were diagnosed with EN in autumn (1 in October and 3 in November), two in winter (in February), three in spring (2 in March and 1 in April) and one in summer (in July) (Table I).

Seven of the patients had fever (above 38.0°C) two to 10 days prior to the development of EN, of whom six had accompanying sore throat and one had accompanying diarrhea (Table I). Six patients with sore throat and fever were diagnosed as tonsillopharyngitis and treated with an antibiotic within the last one month. Two patients received oral ampicillin-sulbactam (Patients 1 and 2); three patients were administered intramuscular benzathine penicillin G (Patient 3, 4 and 9) and one patient received oral azithromycin (Patient 8). One patient with fever and diarrhea was treated with oral trimethoprim-sulfamethoxazole (Patient 6). Of these seven patients who had used antibiotics, three used antibiotics after the development of EN. None of the patients had been exposed to antiepileptics or had recently been vaccinated.

Only two patients had fever when they were diagnosed with EN (Patients 1 and 9). None of the throat cultures of 10 patients included in the study revealed group A beta-hemolytic streptococcus. Of the six patients who had tonsillopharyngitis, recent streptococcal infection was documented in three cases by strongly increased ASO titers (Patients 3, 4 and 9). Their ASO titers were 681, 695 and 708 UI/ml, respectively.

Among the patients included in the study, the duration of the cutaneous changes before admission varied from two to eight days (mean, 3.7±2.1 days). In all children, the EN lesions were located bilaterally on the anterior surfaces of the lower legs; the thighs and the forearms were also involved concurrently in one patient (Patient 6). The size of the lesions varied from 1 cm to 5 cm. Six of them had more than six lesions on each leg.

The tuberculin skin test was positive in two patients and negative in eight. In two cases (aged 8 and 9 years), who had positive tuberculin skin test, induration was above

Table I. Clinical, Epidemiologic and Laboratory Data of the 10 Patients with EN

Patient No.	Sex	Age (y)	Month of diagnosis	Prodromal symptoms	Accompanying symptoms	WBCs 10^9/L (on admit)	NE	ESR (mm/h)	ASO (IU/ml)	CRP (mg/dl)	Tuberculin skin test	Rash duration after admission (days)	Etiology
1	M	7	March	Fever, sore throat	Fever	15.5	86%	24	<40		Negative	4	Not determined
2	F	9	November	Fever, sore throat		16.2	68%	70	<40	5.27	Positive	7	Primary TB
3	F	11	March	Fever, sore throat		9.3	69%	36	681	0.35	Negative	9	Streptococcal tonsillopharyngitis
4	M	12	July	Fever, sore throat		14.7	72%	44	695	0.58	Negative	6	Streptococcal tonsillopharyngitis
5	F	8	November			8.2	67%	22	<40		Negative	10	Not determined
6	F	4	October	Fever, diarrhea		12.5	68%	42	<40	7.26	Negative	7	Not determined
7	F	4	April			4.6	52%	24	<40		Negative	7	Not determined
8	M	11	November	Fever, sore throat		9.9	63%	22	<40		Negative	12	Not determined
9	M	14	February	Fever, sore throat	Fever	26	88%	68	708	33.8	Negative	8	Streptococcal tonsillopharyngitis
10	M	8	February			12.4	67%	30	311	0.63	Positive	12	Primary TB

EN: erythema nodosum. WBCs: white blood cells. NE: neutrophils. ESR: erythrocyte sedimentation rate. ASO: anti-streptolysin-O. CRP: C-reactive protein. TB: tuberculosis.

20 mm, and both cases were asymptomatic in terms of tuberculous infection. Both cases were treated with isoniazid.

No patient had oral or genital aphthae. In one patient, EN was associated with diarrhea. In this patient, stool cultures for Yersinia enterocolitica, Campylobacter, Salmonella and Shigella were negative.

In our study, the mean ESR was 39 mm/h (range, 22-70 mm). It was higher than 40 mm in four patients (40%). The mean total leukocyte count was 12.9×10^9/L (range, 4.6 to 26.0×10^9/L), and six patients had a leukocytosis higher than 10×10^9/L. The mean polymorphonuclear leukocyte (PNL) percentage was 70% (range, 52%-88%). CRP level was studied in six patients and mean level was 7.9 mg/dl (range, 0.3-33.8 mg/dl) (Table I).

All of the patients were restricted from physical activities for a few days and they were advised to elevate their legs[2]. Three patients were treated for streptococcal infection; two patients were administered acetyl salicylic acid and one patient was administered naproxen.

The duration of the recovery of lesions in our cases varied from four to 12 days after admission to our hospital (mean, 8.2±2.6 days) (Table I). In four patients with total leukocyte count lower than 10×10^9/L, the lesions recovered between seven and 12 days (mean, 9.5±2.1 days), and in six patients with total leukocyte count above 10×10^9/L, the lesions recovered between four and 12 days (mean, 7.3±2.6 days). In six patients with ESR lower than 40 mm/h, the lesions recovered between four and 12 days (mean, 9.0±3.1 days), and in four cases with ESR above 40 mm/h, the lesions recovered between six and eight days (mean, 7.0±0.8 days).

The follow-up period varied from three months to two years after the time of EN diagnosis. No recurrence or systemic disease developed in any of the patients.

Discussion

The mean age of EN in childhood is reported around 8-10 years[2,6]. In our study, the mean age of the patients was 8.8±3.3 years (range, 4-14 years).

The sex incidence of children with EN before puberty is known to be approximately equal[2,6,7]. In our patients the ratio of girls and boys was the same.

It has been reported that EN is caused by an immunologic reaction that can be triggered by various antigenic stimuli by bacterial, viral, fungal, chlamydial and parasitic infections, benign or malignant systemic diseases (such as sarcoidosis, enteropathies, Behçet's disease, leukemia, and lymphoma) and drugs[1,3]. In the early reports, childhood EN was most commonly associated with tuberculosis[8]. In the United States and Europe, beta-hemolytic streptococcal infections are currently the most common provoking agents of EN in children[1,2,6,7]; in other parts of the world, tuberculosis, or streptococcal or mycotic infections predominate, depending on the prevalence of these diseases in the community[1].

In our study, none of the throat cultures were determined positive, which could possibly be the consequence of the fact that antibiotics had been used in most of the cases. The diagnosis of recent streptococcal infection was established in three patients (30%) by serodiagnosis. In addition, there were three patients who had had a recent throat infection with no documented streptococcal infection.

Primary tuberculosis was diagnosed in two cases in our study. In recent studies from developed countries, Mycobacterium tuberculosis has been rarely reported as the factor provoking EN[2,3]. EN is seen only in the primary tuberculosis form of tuberculous diseases and appearance of the cutaneous lesions is usually concomitant with the conversion of the tuberculin skin test[1,9]. Mert et al.[9] reported that primary tuberculosis was detected in 20% of the EN-diagnosed cases with known etiology.

While some studies[2,6] have reported non-infectious inflammatory diseases or malignant diseases like enteropathies, sarcoidosis, Behçet's disease and Hodgkin's disease as the causative factor of EN, none of these diseases was detected in our study. Behçet's disease is not rare in Turkey. Tursen et al.[10] found the prevalence of EN among patients with Behçet's disease as 47.6%. Our patients were examined in terms of the presence of oral or genital aphthae, but none was detected in any of the cases. In addition, no finding associated with Behçet's disease was detected.

The etiology of EN could not be determined in 50% of our cases. Similarly, the causative factor of EN could not be determined in 22.2% to 55% of the cases in other studies[2,3,6,7].

In our study, as EN was diagnosed generally in cold seasons, viral respiratory disease could be responsible for those cases.

Use of some antiepileptics and antibiotics and the hepatitis B vaccine have been associated with EN [1-4]. However, none of our cases had used an antiepileptic or had a recent history of vaccination. Four patients had used antibiotics before the development of EN.

The diagnosis of EN can usually be made on the basis of physical examination alone and there is no need for histopathological examination for diagnosis[2,4]. All our cases were diagnosed with EN upon clinical findings. It has been reported that EN lesions most commonly begin to appear on the legs[1] and that nodules may also be observed on the lateral aspects of the lower legs, knees, thighs, forearms, face, neck, or any area of the body with subcutaneous fat[1,2,6]. In our study, the EN lesions were located bilaterally on the anterior surfaces of the lower legs in all children; the thighs and the forearms were also involved concurrently in one patient.

In our study, the mean duration of the rash before admission was 3.7 days (range, 2-8 days). The duration of recovery of EN varied between four and 12 days (mean, 8.2±2.6 days) after admission to our hospital. In the study of Kakourou et al.[2], the mean duration of EN was 11.5±6.5 days (range, 3-60 days), whereas in only three children with Hodgkin's disease, Crohn's disease, and EN of unknown origin it lasted more than 20 days. Similarly, the mean duration of rash was 12 days in the study of Hassink et al.[6] In that study, the mean rash duration was 12 days with infectious diseases, 21 days with noninfectious diseases, and 10 days with no identified associated disease. These findings show that in cases where the rash persists for a longer time, there is an underlying chronic disease such as sarcoidosis due to persisting antigenic stimulus.

In EN cases, acute phase reactants generally increase[1-3,6,11]. In most cases, the ESR was high. Our clinical data were similar to those reported in the literature[2,3,6]. As the number of patients was low in our study, it was not possible to establish a statistical correlation between the increase in acute phase reactants and the causative factor of EN. For the same reason, we also could not establish a statistical correlation between the duration of the recovery of lesions and the high total leukocyte count or increased ESR. However, we think that higher acute phase response does not have a significant impact on the duration of the recovery of lesions.

Recurrence has been reported in some of the EN cases[1-3,6], but there was no recurrence in any of our cases.

In conclusion, this study shows that streptococcal infections are the most common causative factors of EN among children and that tuberculosis is an etiologic factor that should be examined in every EN case in our country.

REFERENCES

1. Bondi EE, Margolis DJ, Lazarus GS. Panniculitis. In: Freedberg IM, Eisen AZ, Wolff K, et al. (eds). Fitzpatrick's Dermatology in General Medicine (5th ed), Vol 1. New York: McGraw-Hill; 1999: 1275-1289.
2. Kakourou T, Drosatou P, Psychou F, Aroni K, Nicolaidou P. Erythema nodosum in children: a prospective study. J Am Acad Dermatol 2001; 44: 17-21.
3. Cribier B, Caille A, Heid E, Grosshans E. Erythema nodosum and associated diseases. A study of 129 cases. Int J Dermatol 1998; 37: 667-672.
4. Fox MD, Schwartz RA. Erythema nodosum. Am Fam Physician 1992; 46: 818-822.
5. Ryan TJ. Erythema nodosum. In: Rook A, Wilkinson DS, Ebling FJ, Champion RH, Burton JL (eds). Textbook of Dermatology (5th ed). Oxford: Blackwell Scientific; 1992: 1931-1938.
6. Hassink RI, Pasquinelli-Egli CE, Jacomella V, Laux-End R, Bianchetti MG. Conditions currently associated with erythema nodosum in Swiss children. Eur J Pediatr 1997; 156: 851-853.
7. Labbe L, Perel Y, Maleville J, Taieb A. Erythema nodosum in children: a study of 27 patients. Pediatr Dermatol 1996; 13: 447-450.
8. Laurance B, Stone DG, Philpott MG, et al. Aetiology of erythema nodosum in children: a study of a group of paediatricians. Lancet 1961; 2: 14-16.
9. Mert A, Özaras R, Tabak F, Öztürk R. Primary tuberculosis cases presenting with erythema nodosum. J Dermatol 2004; 31: 66-68.
10. Tursen U, Gurler A, Boyvat A. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. Int J Dermatol 2003; 42: 346-351.
11. Picco P, Gattorno M, Vignola S, et al. Clinical and biological characteristics of immunopathological disease-related erythema nodosum in children. Scand J Rheumatol 1999; 28: 27-32.