Long-Term Follow-Up of Erythema Nodosum†

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Abstract

One hundred and fifty-four patients with erythema nodosum who attended the skin clinic at Ramathibodi Hospital from January 1990 to December 2000 were evaluated retrospectively with regard to the etiology of erythema nodosum. Of 49 patients who attended the skin clinic during that time 26 returned for reevaluation.

Of the 154 patients, their ages ranged from 10-72 years old; 138 were females, 16 were males. The most common cause of erythema nodosum was tuberculosis (12.3%). Upper respiratory tract infection was found in 3.9 per cent. Other causes included Behcet's disease, sytemic lupus erythematous, drugs, pregnancy, chronic myeloid leukemia, leprosy, Reiter's syndrome and inflammatory bowel disease.

Of the 26 patients who returned for reevaluation, pulmonary tuberculosis was identified in only one patient who had developed erythema nodosum 16 months earlier.

In conclusion, it was found that tuberculosis is still a predominant cause of erythema nodosum among Thai patients.

Key word : Erythema Nodosum, Tuberculosis, Upper Respiratory Tract Infection, Behcet's Disease

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Erythema nodosum (EN) is a cutaneous reaction consisting of inflammatory tender nodolar lesions and is associated with a wide variety of disease processes. The relative frequency of the causative diseases of EN are variable among different studies. The objectives of this retrospective study were to

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evaluate the causes of EN in patients who attended the Division of Dermatology, Ramathibodi Hospital from January 1990 to December 2000 and to reevaluate the patients who were diagnosed as EN in the last 3 years (from January 1998 to December 2000).

METHOD

The medical records of the patients who were diagnosed clinically and histologically with EN were studied retrospectively. The histological diagnosis of EN was established on the basis of the criteria defined by Lever and Schaumberg-Lever, i.e. septal inflammation with inflammation of the septal vessels but without vasculitis[1]. The authors reviewed the medical records of the patients with EN who attended the skin clinic at Ramathibodi Hospital Medical School from January 1990 to December 2000. Data on age of onset, sex, duration of skin lesions, associated diseases, laboratory investigations, chest roentgenogram, tuberculin skin tests and other investigations, treatments and outcome were collected. The patients diagnosed with EN in the last 3 years (from January 1998 to December 2000) were notified by letter to visit the hospital again for reevaluation of the associated diseases. During the visit, clinical history, physical examination, chest roentgenogram, and tuberculin skin test (Monotest, purified tuberculin protein derivative for human use, Pasteur Merieux Connaught) were performed. Tuberculin skin test was interpreted at 72 hours. Erythema and induration more than 10 mm in diameter was interpreted as positive. Other necessary investigations were performed according to the history and physical examination.

RESULTS

A total of 154 records were reviewed. The patients' ages ranged from 10-72 years (mean 33.19 ± 24.92 years old) Table 1. One hundred and thirty-eight patients were females, 16 were males (sex ratio 8.6 : 1). The duration of EN skin lesions ranged from 1 day to 10 years (mean 25.59 ± 127.26 weeks). Most of the lesions (81.3%) appeared on the lower legs. In 29 patients, EN occurred at other sites : both upper extremities (24 patients), thighs and lower legs (3 patients), forearm, and plantar area (1 patient each). The associated diseases or conditions are shown in Table 2. The cause of EN could not be determined in 111 patients (71.6%). The most common cause of EN was tuberculosis (19 patients, 12.3%): pulmonary tuberculosis (9 patients, 5.8%), tuberculosis of lymph nodes (8 patients, 5.2%), papulonecrotic tuberculid (2 patients, 1.3%). Of 9 patients with pulmonary tuberculosis, all of them had an abnormal chest roentgenogram at the first visit with EN. Two of these patients had acid fast bacilli in the sputum. Bronchial biopsy was performed in one patient which revealed granulomatous inflammation with necrotic debris. After a full course of antituberculous drugs, chest roentgenogram returned to normal. Eight patients with tuberculosis of lymph nodes, occurred 1-13 months after onset of EN (mean 7.75 ± 9.1 months) ; such a diagnosis was made from lymph node biopsy or fine needle aspiration (caseous granuloma in 5 patients and necrotizing lymphadenitis in 3 patients). Culture from lymph nodes revealed Mycobacterium tuberculosis in 2 patients and positive acid-fast bacilli was detected in one culture specimen. All the patients were treated with antituberculous drugs. The skin lesions of EN improved within a few weeks of antituberculous drug therapy. Papulonecrotic tuberculid diagnosed clinically and histologically was

Table 1. Age distribution of 154 patients with erythema nodosum.

Age (years)	Number of patients (%)
1-10	1
11-20	18
21-30	61
31-40	33
41-50	25
51-60	11
61-70	3
71-80	2

Table 2. Possible causes of erythema nodosum in 154 patients.

Possible causes	Number of the patients	%
Tuberculosis	19	12.3
Upper respiratory tract infection	6	3.9
Behcet's disease	5	3.3
Systemic lupus erythematosus	3	2.0
Drugs	3	2.0
Pregnancy	3	2.0
Borderline tuberculoid leprosy	1	0.7
Reiter's syndrome	1	0.7
Inflammatory bowel disease	1	0.7
Chronic myeloid leukemia	1	0.7
Unidentified cause	111	71.6

Table 3. Results of tuberculin skin test in the patients with and without tuberculosis.

	Positive	Negative
Patients with tuberculosis	14	1
Patients without tuberculosis	51	30

found in 2 patients. It developed after onset of EN 10 months and 1 year respectively. The skin lesions of papulonecrotic tuberculid and EN disappeared after treatment with antituberculous drugs. Tuberculin skin test was performed in 15 of 19 patients with tuberculosis (Table 3). The result was strongly positive in 14 patients (93.3%), with a mean diameter of reaction = 27.42 ± 38.54 mm. The tuberculin skin test was negative in one patient with pulmonary tuberculosis. Among the patients without tuberculosis, tuberculin skin test was performed in 81 patients, a positive reaction was found in 51 patients (63%) (the mean diameter of reaction = 21.07 ± 20.3 mm). In Table 3, sensitivity of tuberculin skin test was 93 per cent, and specificity was 37 per cent, (positive predictive value 21.5%, negative predictive value 96.8%).

Upper respiratory tract infection was associated with EN in 6 patients and EN resolved spontaneously in a short period of time.

Behcet's disease was diagnosed in 5 patients who had recurrent aphthous ulcers at least 3 times in one 12-month period and had at least 2 criteria as suggested by the International criteria for Behcet's disease[2]. EN occurred preceding, concomitant or following Behcet's disease. In most of the patients, EN was recurrent and difficult to treat.

Three patients had systemic lupus erythematosus (SLE) associated with EN. Furthermore, EN developed concomitantly with SLE in one patient and occurred after onset of SLE in two patients. One of the patients had recurrent EN, while two other patients had only one episode of EN.

Drugs were the causative agents of EN in 3 patients. These drugs consisted of piroxicam, mefenamic acid and orphenadrine citrate plus paracetamol; EN disappeared within a week after drug discontinuation.

Three patients were pregnant and developed EN at 20-37 weeks of gestation (mean 29.6 weeks).

Four patients had EN in association with inflammatory bowel disease, borderline tuberculoid leprosy, chronic myeloid leukemia and Reiter's syndrome respectively. EN resolved after the treatment of associated diseases in all except one patient who had Reiter's syndrome. This patient developed recurrent EN that did not respond well to any treatment.

In most of the patients with unidentified cause, EN responded well to treatments and resolved within a few weeks.

There are many modalities for the treatment of EN. Some patients received more than one kind of treatment due to the recurrent and chronic course of EN. The most common treatment in the presented patients was antituberculous drugs followed by non-steroidal anti-inflammatory drugs (NSAIDs) which included indomethacin, piroxicam, ibuprofen and naproxen. Other treatments included colchicine, systemic and topical corticosteroids, dapsone and saturated solution of potassium iodide (SSKI) (Table 4). Only 19 patients were definitely diagnosed with tuberculosis. Other patients received antituberculous drugs because of their positive tuberculin skin test. Among the group treated with antituberculous drugs, 40 of 47 patients (85.1%) responded well and EN resolved completely. Non-steroidal anti-inflammatory agents

Table 4. Treatment of erythema nodosum.

Treatment	Number of patients treated	Number of patients who responded to treatment	%
Antituberculous drugs	47	40	85.1
NSAIDS	45	36	80.0
Colchicine	22	11	50.0
Prednisolone	15	12	80.0
Topical corticosteroids	2	1	50.0
Dapsone	8	2	25.0
Saturated solution of potassium iodide (SSKI)	2	0	0

and prednisolone were also effective treatment for EN with an 80 per cent response rate (Table 4). Colchicine, topical corticosteroid, dapsone and SSKI did not work well in this group of patients.

After an attempt to contact 49 patients who had EN in the last three years, only 26 patients (25 female, 1 male) responded and visited the clinic for further evaluation. Associated diseases were identified in 2 patients from the first visit in the past three years. One patient had tuberculosis of the lymph nodes, and another one had inflammatory bowel disease. All the 26 patients were healthy with resolved EN and their underlying diseases. The patient who had inflammatory bowel disease denied chest roentgenogram and tuberculin skin test. As for the remaining patients, tuberculin skin test was negative. Chest roentgenogram was abnormal in one patient (not the same one who had tuberculosis of the lymph nodes) and was interpreted to be probably caused by tuberculosis. She had developed EN 16 months earlier. After receiving antituberculous drugs for 3 months, she was lost to follow-up.

DISCUSSION

Of the 154 patients in this study, there was a female preponderance (ratio 8.6 F : 1 M), compatible with other published studies[3-5]. The reason for female preponderance in EN remains unknown. It is interesting that in children, there is no such preponderance[6]. Female hormones may directly cause EN or indirectly modify the immune status of the patients[7], and make them more vulnerable to various antigenic stimuli. Most of the patients in the present study were between the second and fourth decade, with the peak incidence between 21 and 30 years of age, similar to previous studies[3,8].

The most common cause of EN in the present study was tuberculosis (12.3%), which is still endemic in Thailand. These patients had either tuberculosis of the lungs or lymph nodes ; two patients had papulonecrotic tuberculid. This study differs from other studies which reported that upper respiratory tract infection (Streptococcal or non Streptococcal infection) was the most common cause of EN[3-6]. Tuberculosis might be detected concomitantly with EN or develop 1-13 months after the onset of EN. In the present long-term follow-up of 26 patients, pulmonary tuberculosis was detected in one patient 16 months after onset of EN. The second and third most common causes of EN in the present study were upper respiratory tract infection (3.9%) and Behcet's disease (3.3%) (Table 2). Other associated conditions of EN in the present series included systemic lupus erythematous, drugs, pregnancy, borderline tuberculoid leprosy, Reiter's syndrome, inflammatory bowel disease, chronic myeloid leukemia. The cause of EN could not be identified in 71.6 per cent of the patients.

The medical approach for patients with EN should include complete history, physical examination (especially searching for lymphadenopathy), chest roentgenogram, tuberculin skin test, throat swab culture, two consecutive determinations of antistreptolysin O (ASO) titer in a 2-4 week interval and other necessary laboratory investigations as suggested by clinical findings. Tuberculin skin test is still useful as a screening test especially in an endemic area. The sensitivity of this test was 93 per cent, the specificity was 37 per cent in the presented patients. The sensitivity of the tuberculin skin test in other studies varied from 61-81 per cent[9-12]. The false negative reaction in one patient in the present study may be due to severe illness or malnutrition which may cause non-specifically reduced delayed hypersensitivity reaction. However, the authors did not repeat the tuberculin skin test in this patient because of clinical improvement. In a group of patients with EN who did not have evidence of tuberculosis, 51 of 81 patients (63%) had a positive reaction to the tuberculin skin test. The 47 patients in this group who had a strong positive reaction (erythema and induration more than 15 mm in diameter) were treated with isoniazid for one year, 40 patients (85.1%) responded well to treatment and EN resolved completely. Others had recurrence of EN after one year of isoniazid therapy. Unfortunately, these seven patients were lost to follow-up, so further investigation was not possible.

In the present study, the patients with EN who did not have infectious disease responded well to non-steroidal anti-inflammatory agents and prednisolone with 80 per cent response rate. Other modalities of treatment such as colchicine, topical corticosteoid, dapsone and SSKI were not effective, with only 0-50 per cent response rate.

In a long-term follow-up of 26 patients with EN, only one patient had a abnormal chest roentgenogram which was probably tuberculosis. She had been diagnosed with EN 16 months previously. Unfortunately, no sputum examination was performed, the tuberculin skin test was negative and she failed to attend the follow-up clinic after 3 months of antituber-

culous drugs. There was no definite proof of pulmonary tuberculosis in this patient.

In conclusion, of 154 patients with EN, tuberculosis was the most common cause (12.3%) followed by Streptococcal or non Streptococcal respirating tract infection (3.9%) and Behcet's disease (3.3%), respectively. No etiology accounted for 71.6 per cent of the presented patients. Complete history and physical examination (especially palpation of lymph nodes) is necessary to identity the cause of EN. Chest roentgenogram and tuberculin skin test are essential in endemic areas of tuberculosis. The patients need long-term follow-up, at least 18 months, after the onset of EN to make sure that they do not develop tuberculosis. The role of isvariazid for prevention of tuberculosis in patients with EN is still controversial. Further study should be performed to evaluate this kind of treatment. In the idiopathic cases, non-steroidal anti-inflammatory drugs and prednisolone are more effective than colchicine, topical corticosteroid, dapsone and saturated solution of potassium iodide (SSKI).

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การติดตามดูผู้ป่วยอีริธีมา โนโดซุม ในระยะยาว

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คณะผู้วิจัยได้ศึกษาย้อนหลังผู้ป่วยที่เป็นอีริธีมา โนโดซุม (Erythema Nodosum (EN)) จำนวน 154 ราย ซึ่งมาตรวจรักษาที่คลินิกโรคผิวหนัง โรงพยาบาลรามาธิบดี ตั้งแต่เดือนมกราคม พ.ศ. 2533 ถึงเดือนธันวาคม พ.ศ. 2543 เพื่อศึกษาสาเหตุของ EN ใน จำนวน ผู้ป่วย EN 49 ราย ซึ่งมาตรวจรักษาตั้งแต่เดือนมกราคม พ.ศ. 2541 ถึงเดือนธันวาคม พ.ศ. 2543 ผู้ป่วย 26 ราย สามารถกลับมาตรวจซ้ำได้อีกเพื่อหาสาเหตุของ EN

ในจำนวนผู้ป่วย 154 ราย มีอายุระหว่าง 10-72 ปี เป็นผู้หญิง 138 ราย ผู้ชาย 16 ราย สาเหตุของ EN ที่พบบ่อยที่สุดคือวัณโรค (12.3%) การติดเชื้อในทางเดินหายใจพบ 3.9% สาเหตุอื่นของ EN ที่พบ ได้แก่ Behcet's disease, systemic lupus erythematsus, ยา, การตั้งครรภ์, chronic myeloid leukemia, โรคเรื้อน, Reiter's syndrome และ inflammatory bowel disease

ในจำนวนผู้ป่วย 26 ราย ที่สามารถกลับมาตรวจซ้ำได้อีก พบวัณโรคปอด 1 ราย ซึ่งเป็น EN มาก่อนการตรวจพบวัณโรคปอด 16 เดือน

โดยสรุป พบว่าวัณโรคเป็นสาเหตุสำคัญที่สุดของ EN ในผู้ป่วยไทยที่มาตรวจรักษาที่โรงพยาบาลรามาธิบดี

คำสำคัญ : อีริธีมา โนโดซุม, วัณโรค, การติดเชื้อทางเดินหายใจส่วนบน, โรคเบเซท

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