Erythema nodosum: an evaluation of 100 cases

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Abstract

Objective

In this study, we investigated the clinical features, etiology, and also predictive factors of secondary erythema nodosum (EN) in patients with EN.

Method

A total of 100 patients (mean age: 37 years) diagnosed with EN between 1993 and 2004 in our clinic were included in the study prospectively. A skin biopsy was performed in 46 of the patients. Patients were considered to have secondary EN when an underlying condition was found, and to have primary EN when no such condition was found. For the diagnosis of the underlying diseases, the pertinent diagnostic criteria and/or diagnostic methods were used. Categorical and continuous variables were compared by using chi-square and Mann-Whitney U tests respectively. Multiple regression analysis was applied to the significantly different variables.

Results.

The majority of the patients were female (female/male: 6/1) and nearly half (47%) of the cases had a determined etiology. The leading etiology was poststreptococcal (11%), followed in decreasing order by primary tuberculosis (10%), sarcoidosis (10%), Behçet's syndrome (BS) (6%), drugs (5%), inflammatory bowel diseases (IBD) (3%), and pregnancy (2%). Fifteen (15%) patients complained of cough; the diagnosis was primary tuberculosis in eight cases and sarcoidosis in seven. Four patients with arthritis were diagnosed as having BS (in 3) and Crohn's disease (in 1). All the patients were followed for a mean duration of 4.5 years. The nodosities relapsed annually in 62% (33/53) of idiopathic EN patients but in only one (BS) in the secondary EN group. The histology was consistent with EN in all biopsied patients. Our study revealed that fever, leukocytosis, elevated CRP level, accelerated ESR, presence of cough, sore throat, diarrhea, arthritis, and pulmonary pathology were predictors of secondary EN. Recurrence in EN significantly predicted primary EN. All of the patients had bed rest and the majority was given an anti-inflammatory agent (naproxen sodium). The outcomes were usually favorable within 7 days. The patients with an underlying disease were given the specific treatment.

Conclusion

EN has been associated with numerous diseases. In order to reduce cost and duration of diagnosis, every centre should determine its own most frequent etiologic factors. Predictive variables for secondary EN should also be determined and an optimum management for such patients should be clarified. Our study revealed streptococcal pharyngitis, primary tuberculosis, sarcoidosis, IBD, and BS as the main etiologies of EN.

Key words

Erythema nodosum, etiology, predictive factors.

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Introduction

Erythema nodosum (EN) is the most frequent form of panniculitides. It is a red, very tender and nonulcerating nodule of the lower extremities and especially pretibial regions that usually involutes within 3 to 6 weeks. The classic histology is an acute septal panniculitis of subcutaneal fat lobule without signs of true vasculitis (1). It is considered a late type hypersensitivity reaction to several antigenic stimuli generally developing after 3 to 6 weeks (1, 2). The incidence (in northwestern Spain, ≥ 14 year-old ones ~ 5/100.000, in the Negev region of Israel 2/100.000) and etiology vary according to the geographic regions (1-4).

EN panniculitis is among the differential diagnosis of the other panniculitides which are all tender erythematous nodules (1, 2, 5, 6). For this reason, a skin biopsy is required to confirm the diagnosis (1, 2).

The aims of this study are: 1) to determine clinical and laboratory features of EN, 2) to describe the etiology, 3) to determine the factors favoring primary and secondary, and 4) to compare the etiology with the series reported from Europe, the Middle East, and Asia. The first 50 cases of our study have been published previously (7).

Patient and methods

One hundred adult (> 16 years old) patients admitted with tender erythematosus nodosities located on the legs and diagnosed clinically as EN during the last 12 years (between 1993 and 2004) were enrolled in the study prospectively. The specific aim for performing the study prospectively was to determine the clinical course and to detect any recurrences of the nodosities. The demographic features (age and sex) and the month admission were determined. All patients were questioned in detail and a thorough physical examination was done especially considering the disorders leading to EN. Since the other panniculitides may lead to lesions similar to EN, a skin biopsy including cutaneous and subcutaneous tissues was performed upon patients' consent.

Classification of EN: EN was classified as primary when an etiology which may lead to EN was not detected or as secondary when there was an underlying disorder. The disorders that may lead to EN were diagnosed by the following criteria:

1. Behçet's syndrome (BS): All patients were questioned for oral aphthae, and when described, the diagnostic criteria for BS established by the International Study Group for Behçet's Disease (in the presence of oral aphthae, presence of at least two of the following: recurrent genital ulcers, eye involvement, skin involvement, and a positive pathergy test) were used (8).

2. Poststreptococcal EN: For the patients describing sore throat within the last 3 weeks, the following criteria were used (9); a positive throat swab culture or a positive rapid antigen detection test or an anti-streptolysin (ASO) result in high or increasing titers.

3. Primary tuberculosis (TB): All patients had a chest x-ray. In patients who had hilar mass and/or mediastinal enlargement on chest x-ray or had a complaint of cough, a thorax CT was obtained. When parenchymal infiltration and hilar and/or mediastinal lymphadenopathy (LAP) were seen in CT, bronchoscopy, bronchoalveolar lavage (BAL), and when indicated bronchial biopsy were obtained. BAL fluid was investigated for acid-fast bacilli and cultured for TB bacilli. When these diagnostic measures failed, mediastinoscopy and excisional lymph node biopsy were performed. A tuberculin skin test was applied to all patients.

4. Sarcoidosis: The consistency of clinical, radiologic, and histopathologic (noncaseating granulomas) characteristics was required (10).

5. Inflammatory bowel disease (ulcerative colitis and Crohn's disease): For the patients with gastrointestinal complaints such as diarrhea and abdominal pain, radiological-endoscopic studies were performed. A definitive diagnosis was established by tissue sampling.

All patients were questioned for drug use in the preceding month and for common cold or flu in the preceding week.

Relapse (recurrence): in a patient with EN, it was defined as the re-emergence of erythematous nodosities after a disease-free period of at least one month (3).

Laboratory studies

Complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver function tests, and anti-streptolysin O (ASO) were studied. Tuberculin skin test was applied to 63 patients, especially including the ones who had radiological studies suggesting primary TB or sarcoidosis. The diameter of the induration was measured 48 hours later. An ophthalmic examination was obtained for the patients presumed to have sarcoidosis or BS. The patients were followed in an outpatient unit. Follow-up data were obtained by phone calls from those who were unable to attend follow-up visits.

Treatment

All patients were treated according to their lesions and to the underlying disorder in secondary EN.

Statistical analysis

Clinical and laboratory features of the patients with primary EN were compared to those with secondary EN in order to determine the factors predicting secondary EN. Categorical variables were expressed as a percentage and continuous variables in mean ± SD. Categorical and continuous variables were compared by using chi-square and Mann-Whitney U tests respectively. A p level ≤ 0.05 was considered statistically significant. Multiple regression analysis was applied to the variables which were found to be significant.

Results

Demographic, seasonal, and etiologic features of 100 patients with EN are shown in Table I. The majority was female in child-bearing age (female/male: 6/1). When the patients were evaluated as a whole without regarding the etiology, 66% were seen to develop within the first six months of the year.

Clinical and laboratory features of the patients are given in Table II. All the patients had red, tender, erythematous nodosities on the pretibial region measuring 1 to 25 cm and 2 to 40 in number. All but one was bilateral. In 11 patients, there were nodosities in the other parts of the body (knee, thigh, forearm, arm, and trunk). Fifteen (15%) complained

Table I. Demographic, seasonal, and etiologic features of our 100 patients with erythema nodosum.

Etiology (n;%)	Mean age ± SD (range) (in years)	Female/male	The relative rate in first 6 months of the year
Primary (n = 53; 53%)	43 ± 13 (27-71)	51/2	57%
Secondary (n = 47; 47%)	32 ± 11 (15-56)	33/14	76%
1. Poststreptococcal (n = 11, 11%)	(16-44)	10/1	
2. Primary TB (n = 10, 10%)	(16-37)	7/3	
3. Sarcoidosis (n = 10, 10%)	(21-56)	9/1	
4. Behçet's syndrome (n = 6, 6%)	(17-41)	1/5	
5. Drugs (n = 5, 5%)	(22-59)	2/3	
6. Pregnancy (n = 2, 2%)	(26 and 35)	2F	
7. Crohn's disease (n = 2, 2%)	(23 and 47)	2F	
8. Ulcerative colitis (n = 1, 1%)	(37)	1F	
Total: 100	37 ± 13 (15-71)	84/16	66%

Table II. Clinical and laboratory features of the patients with erythema nodosum.

Clinical feature	No. of patients (n = 100)	Rate (%)
Bilateral, pretibial, painful, red nodosities	99	99
Fever	34	34
Arthralgia	45	45
Fatigue	31	31
Cough	15	15
Weight loss	20	20
Diarrhea	4	4
Arthritis	4	4
Sore throat	11	11
Leukocytosis (≥10.000/mm^3)	14	14
Erythrocyte sedimentation rate (mm/hour)		
Normal	18	18
20-49	39	39
50-99	31	31
≥ 100	12	12
CRP (quantitative)		
Normal	41	41
< 6 x ULN	38	38
7-11 x ULN	8	8
≥ 12 x ULN	13	13

ULN: upper limit of normal.

Table III. Diagnostic methods in the patients with poststreptococcal erythema nodosum.

Patient no/ age/sex	History of sore throat	GAS in throat swab culture	ASO (Normal:0-200 U/ml)
1/39/F	14 days ago	Negative	1000
2/44/F	21 days ago	Negative	1458
3/18/F	17 days ago	Negative	600
4/32/F	14 days ago	Positive	440
5/34/F	14 days ago	Negative	482
6/30/F	7 days ago	Negative	264 525 (7 days later)
7/38/F	21 days ago	Negative	165 1600 (14 days later)
8/40/M	7 days ago	Not performed	800
9/18/F	7 days ago	Negative	350
10/28/F	14 days ago	Negative	262
11/25/F	7 days ago	Negative	900

F:female, M:male, GAS: group A β-hemolytic streptococcus, ASO: anti-streptolysin O.

Table IV. Diagnostic methods in the patient with primary tuberculosis.

Patient no/ Age/Sex	Chest x-ray	Tuberculin skin test	Thorax CT	Other diagnostic methods
1/17/M	Right hilar LAP	40x30 mm	BHL, infiltration in right upper lobe anterior segment	Biopsy of bronchial mucosa: non-caseating granulomas
2/33/F	Right hilar LAP	23x20 mm	Right hilar and mediastinal LAP	BAL fluid yielded TB bacilli
3/22/F	Right hilar LAP	20x25 mm	Right hilar LAP	BAL fluid yielded TB bacilli
4/26/F	Normal	20x25 mm	Right hilar and mediastinal LAP	BAL fluid yielded TB bacilli
5/18/M	Right hilar LAP	20x20 mm	Right paratracheal and right intrapulmonary LAP, infiltration in right upper lobe posterior segment	
6/16/F	Right hilar LAP	15x12 mm	Right paratracheal and intrapulmonary LAP	
7/18/F	Right hilar infiltration	28x30 mm	Cavitation and surrounding infiltration in right lower lobe superior segment	Sputum yielded TB bacilli
8/37/F	Normal	20x18 mm	Multiple mediastinal LAP+ milimetric nodules in right upper lobe apical and anterior segments, middle lobe medial and lateral segments	
9/28/M	BHL	(-)	Multiple mediastinal LAP+ nodules (< 1 cm) in right upper lobe	BAL fluid yielded TB bacilli Mediastinoscopic excisional LAP biopsy: caseating granulomas
10/22/F	Normal	20x20 mm	Multiple mediastinal LAP+ infiltration in left upper lobe	BAL fluid did not yield TB bacilli

M:male; F: female; LAP: lymphadenopathy; BHL: bilateral hilar lymphadenopathy; BAL: bronchoalveoler lavage; AFB: acid fast bacilli.

Table V. Diagnostic methods in the patients with sarcoidosis.

Patient no/ Age/Sex	Chest x-ray	Tuberculin skin test	Thorax CT	Other diagnostic methods
1/42/F	Left hilar LAP	Negative	BHL+multiple mediastinal LAP	Transbronchial biopsy: noncaseating granulomas
2/56/F	Normal	10x10 mm	BHL	Transbronchial biopsy: noncaseating granulomas
3/30/F	BHL	Negative	BHL	Transbronchial biopsy: noncaseating granulomas
4/55/F	BHL	10x10 mm	BHL	Transbronchial biopsy: noncaseating granulomas
5/30/E	BHL and solitary pulmonary noduls	Negative	Mediastinal LAP and pulmonary nodules	Mediastinoscopic biopsy: noncaseating granulomas
6/21/K	BHL	Negative	Mediastinal LAP and pulmonary nodules	Mediastinoscopic biopsy: noncaseating granulomas
7/42/K	BHL	Negative	BHL and mediastinal LAP	Mediastinoscopy and transbronchial biopsy can not be performed for the last 4 patients
8/17/K	Normal	9x9 mm	BHL and mediastinal LAP	
9/50/K	BHL	Negative	BHL and mediastinal LAP	
10/40K	BHL	Negative	BHL and mediastinal LAP	

BHL: bilateral hiler lenfadenopati.

from cough and primary TB and sarcoidosis were diagnosed in 8 and 7 respectively. Four patients with arthritis were diagnosed as BS (n = 3) and Crohn's disease (n = 1). Liver transaminases were normal in all. Tuberculin skin test was positive (an induration of > 10 mm) in 36 out of 63 (57%).

In 47 of the cases, the etiology was determined and poststreptococcal EN was the leading cause (11%) followed by primary TB (10%), sarcoidosis (10%), BS (6%), drugs (5%), inflammatory bowel disease (3%), and pregnancy (2%).

The diagnostic methods in poststreptococcal EN patients are given in Table III. Throat swab culture was studied in 10 patients and yielded β-hemolytic streptococci in one. All the culture-negative patients reported use of beta-lactam antibiotics for their sore throat diagnosed as streptococcal tonsillopharyngitis.

The diagnostic methods in primary TB patients are given in Table IV. All but one was given quadruple anti-TB therapy (isoniazid-INH, rifampin-RIF, pyrazinamide-PZA, and ethambutol-EMB) and all began to respond clinically within 3 weeks. INH+RIF were given at least 6 months, and PZA+EMB two months. One patient denied treatment; during follow-up a spontaneous improvement by clinical and radiological (thorax CT at 6th month) features was detected.

Table VI. Diagnostic methods in the patients with Behçet's syndrome.

Patient no/ Age/Sex	Recurrent oral aphthae	Recurrent genital ulcer	Eye involvement	Skin involvement	Patergy test
1/41/M	Positive	Positive	Negative	EN	Negative
2/33/M	Positive	Positive	Negative	EN	Negative
3/27/M	Positive	Positive	Negative	EN	Pozitive
4/33/M	Positive	Positive	Negative	EN	Pozitive
5/24/F	Positive	Positive	Positive (iridosiclitis)	EN	Negative
6/28/M	Positive	Positive	Positive (iridosiclitis)	EN	Negative

Table VII. Comparative analysis of continuous and categorical variables in the patients with primary or secondary EN.

Clinical feature	Idiopathic EN	Secondary EN	*p* value
Continuous variables			
Leukocyte count /mm^3	6898 ± 1526	8940 ± 2668	0.000
ESR (mm/saat)	28 ± 18	62 ± 37	0.000
CRP (mg/dl)	13 ± 23	48 ± 56	0.000
Categorical variables			
Fever	6	28	0.000
Recurrence in EN	33	1	0.000
Cough	1	14	0.000
Sore throat*	0	11	0.000
Artritis	0	4	0.042
Diarrhea	0	4	0.042
Abnormal chest x-ray	0	13	0.000

EN: erythema nodosum; ESR: erythrocyte sedimentation rate. *One to three weeks preceding the onset of EN.

Sarcoidosis was diagnosed in 10 patients; the diagnostic methods are given in Table V.

BS was diagnosed in 6 cases. The diagnostic methods for these cases are summarized in Table VI. The patients reported recurring oral aphthae 3 to 12 times yearly within recent 1 to 4 years, healing generally within 7 days. All reported genital ulcers for 9 months to 2.5 years healing with cicatrix. Five had folliculitis and half had oligoarticular arthritis.

Use of drugs (amoxicillin/ clavulanate, cefuroxime axetil, ciprofloxacin, a combination of phenylpropanolamine + paracetamol + chlorpheniramine maleate, and fluvastatin) was considered as the etiology in 5 EN patients. EN developed 1 to 2 weeks after the use of these drugs and also regressed 2 to 3 weeks after the discontinution. Fluvastatin was re-administered and EN recurred 7 days after this rechallenge.

The etiology was determined as Crohn's disease in two patients and ulcerative colitis in one. A 37-year-old woman, followed with the diagnosis of spastic colon for 6 years was hospitalized with a 3-week fever, increased intestinal complaints, and bilateral, painful, pretibial nodosities. On questioning, she reported oral aphthae for 10 years, relapsing 3 times annualy and healing spontaneouly within 7 days. An active ulcerative colitis was diagnosed by biopsy through recto-sigmoidoscopy. The second case presented with second relapse of painful nodosities within the last year. The history revealed enterocolitis type diarrhea and colonoscopy + biopsy diagnosed Crohn's disease. The patients were referred to the relevant units.

Our two patients developed EN during their course of pregnancies (3rd and 6th months) and the nodosities regressed within 2-3 weeks by bed rest. After delivery, the nodosities did not recur in a period of 1 year.

All the patients were followed in a mean period of 4.5 ± 4 years (range: 6 months-10 years). Nodosities recurred in 62% (33/53) of idiopathic EN patients every year. Additionally, these patients reported previous recurring painful nodosities for a mean duration

Table VIII. The etiologic categories in published EN series.

Etiology	Erez *et al.*[4] (1973-1982) (50 patients) %	Cribier *et al.*[11] (1960-1995) (129 patients) %	Garcia-Porrua *et al.*[3] (1988-1997) (106 patients) %	Psychos *et al.*[12] (1984-1990) (132 patients) %	Puavilai *et al.*[10] (1982-1992) (100 patients) %	Our series (1993-2004) (100 patients) %
I - Idiopathic	32	55	37	35	72	53
II - Secondary	68	45	63	65	28	47
1-Streptococcal	44	28	8	6	6	11
2-Primary TB	2	1	5	2	12	10
3-Sarcoidosis	2	11	20	28	0	10
4-Drugs	10	0	3	4	7	5
5-Behçet's syndrome	0	0	2	4	3	6
Country	İsrael	France	Spain	Greece	Thailand	Turkey

of 12 ± 10 years (range: 3-42 years).

In all of the 46 cases, biopsy results confirmed the clinical diagnosis of EN.

The factors predicting secondary EN are given in Table VII. All the variables compared by Mann-Whitney U and chi-square tests between primary and secondary EN groups had significant differences. Multiple regression analysis (with enter method) revealed that fever ($p < 0.001$), leukocytosis ($p < 0.001$), elevated CRP level ($p = 0.001$), accelerated ESR ($p < 0.001$), presence of cough ($p < 0.001$), sore throat ($p < 0.01$), diarrhea ($p < 0.05$), arthritis ($p < 0.05$), and pulmonary pathology ($p < 0.001$) were predictors of secondary EN. Recurrence in EN ($p < 0.001$) significantly predicted primary EN. When a stepwise forward conditional method was used, the combination of fever and non-recurring EN was seen to be the most significant parameters predicting secondary EN.

All the patients except the pregnant ones were maintained at bed-rest and given naproxen (1000 mg/day, 2 to 3 weeks). A clinical improvement was generally obtained within 7 days. Five patients did not respond to naproxen , were switched to oral potassium iodine (900 mg/day) and responded within 7 days.

Nineteen patients with a noninfectious etiology were transferred to the relative units. Twenty-one patients with an infectious etiology were initiated on specific therapy.

Dıscussıon

The clinical heterogeneity and the possible different underlying pathogenic mechanisms responsible for the development of EN in different diseases presenting with EN may explain the weak association reported so far between specific genetic markers and EN. In this regard, although idiopathic and some groups of secondary EN seem to have different HLA-DRB1 association (11) and association between macrophage migration inhibitory factor and E-selectin gene polymorphisms in patients with sarcoidosis associated EN compared with the rest of patients with EN has been described (12, 13), this was not the case for other genetic polymorphisms (14).

Age and sex distribution in EN is related with whether it is idiopathic or secondary (1, 2, 7). Idiopathic cases are generally seen in females in child-bearing age; female/male ratio is reported as 3-6/1. A relationship between idiopathic EN and estrogen has been reported. Relatively frequent occurrence of EN in females in child-bearing age, in the first and second trimester of the pregnancy and in those using oral contraceptives containing high doses of estrogen support this theory. For the patients with a known etiology, age and sex distribution are correlated with the related disorders. When our patients were evaluated as a whole without regarding the etiology, the mean age was 37 and the majority was female (F/M: 6/1).

Medical literature reported an accumulation in the first 6 months of the year among the patients with EN (2). When our patients were evaluated as a whole without regarding the etiology, 2/3 of the patients presented in the first 6 months of the year.

EN panniculitis is among the differential diagnosis of the other panniculitides (erythema induratum of Bazin, nodulary vasculitis, cutaneous polyarteritis nodosa, and subcutaneous lymphoma) which are all tender erythematous nodules (1, 2, 6). For this reason cutaneal and subcutaneal biopsy is recommended to confirm the diagnosis (1-3).

The classical histopathology is an acute septal panniculitis without vasculitis (1, 2). The early finding is neutrophilic infiltration. The late finding is Miescher's microgranulomatous focus constituted of histiocytic giant cells and lymphohistiocytes.

A major limitation of this study might be the relatively low frequency of biopsy-proven patients diagnosed with septal panniculitis. However, in the present series, experienced clinicians saw all the cases. In addition, an extended follow-up of these patients allowed us to exclude conditions different from EN presenting as panniculitis.

A biopsy was performed in 46 cases diagnosed by clinical findings and all gave a consistent histology. The biopsy is the proof of the disease. However, when the etiology is evident (post-streptococcal EN, primary TB, sarcoidosis, and BS) it may not be necessary. Moreover, if a patient gives a history of recurrent, pretibial nodosities for several years, the biopsy may not contribute much to the diagnosis. Briefly, in patients reporting recurring EN for years and/or an etiology is easily defined, biopsy may not be performed.

In the clinical series of EN, an etiology can be found in nearly half of the cases. The majority of the etiologies in these cases are, in decreasing order, infections (especially streptococcal pharyngitis and primary TB), sarcoidosis, drugs, BS, and inflammatory bowel diseases (Table VIII) (3, 4, 15-17). On the other hand, many disorders are listed among the rare causes of EN (1-4, 9, 15-18). One of them, yersiniosis, although rare in our country (19), is a prevalent infectious disease in northern European countries (20).

Streptococcal pharyngitis is the most frequent etiology of EN all over the world (both in developed and developing countries) (3, 4, 15-18). Development of EN 1 to 4 weeks after pharyngitis is a well-known phenomenon. For every patient with EN, a detailed history of tonsillitis (a diagnosis by a physician or sore throat) in the preceding month should be taken. When the history is positive, a previous infection should be verified by one of the diagnostic methods used in this disease (9). Eleven percent of our cases had a history of streptococcal pharyngitis.

Among the clinical forms of TB, primary TB is unique to cause EN (1, 2, 21, 22). EN due to primary TB is frequently seen in children and young adolescents (<20 years) in whom primary TB itself is frequent (21).

Radiological findings of primary TB include parenchymal (right upper lobe anterior segment or right middle lobe medial segment) and/or intrathoracic LAP (hilar and/or mediastinal) involvement (21-27). Additionally, in nearly 15% of the cases with primary TB, bilateral hilar LAP is also seen (21, 25, 26, 28). Radiological findings of our ten patients with primary TB are described in Table IV in detail.

TB is moderately endemic in our country. All over the world, TB remains to be a health problem especially in the developing countries (21). For this reason, every patient with EN should be screened for primary TB. Previous studies showed that primary TB was a common etiology of EN in the countries where TB is endemic and that it was an uncommon etiology in the developed countries (Table VIII) (3, 4, 15, 16). We found it to be a major etiology.

When all the regions of the world are considered as a whole, sarcoidosis is the second cause of EN following infections (Table VIII) (3, 4, 15-17). Although sarcoidosis is a frequent etiology in European studies, it is a rather rare in Middle East and Southeastern Asia (3, 4, 15-17). This finding is a result of differences in sarcoidosis prevalence among localizations. Sarcoidosis prevalence differs significantly (1-64 / 100.000) in various parts of the world. Although its prevalence is 10-40/100.000 in USA and Europe, it is extremely rare in Africa and Southeastern Asia (10). Its prevalence in our country is not exactly known. It may be expected to be between the figures of Asia and Europe. For typical cases, the diagnosis can be established by the consistency of clinical, radiological, and histopathological (noncaseating granulomas) findings (6, 27). EN due to sarcoidosis is frequently together with bilateral hilar lymphadenopathy (BHL) (Löfgren's syndrome) (28). However, in a case of EN with BHL, in the countries where TB is endemic, besides sarcoidosis, primary TB should also be considered.

In patients with sarcoidosis, skin involvement is seen in 25% of the cases, EN being the most frequent one (7, 29, 30). In the present study, sarcoidosis was the etiology in 10% of the cases. All these patients had radiological (chest x-ray and/or thorax CT) findings of BHL and/or mediastinal LAP.

EN is seen in half of the cases with BS (31). The prevalence of this syndrome is high in our country (80-300/100,000) (31, 32). For the diagnosis, the criteria of International Study Group for Behçet's Disease are used (8). The criteria are based on clinical (history and physical examination) features. For this reason, in the etiology of EN, this disease should be excluded initially. The absence of oral aphthae easily makes the diagnosis unlikely. BS was found as the etiology of EN in 6% of our cases according to the criteria of International Study Group and referred to the related unit.

Although many drugs may lead to the formation of EN, oral contraceptives, antibiotics, aspirin, non-steroid anti-inflammatory drugs, and iodine compounds are responsible for the majority of the events (33). Among the EN series, drugs have been the fourth most frequent etiology with a rank of 5% (0 to 10%) (Table VIII). Accordingly, it corresponded to 5% of our cases. Our patients described emergence of EN 1 to 2 weeks after taking the drugs (antibiotics, fluvastatin) and a rapid resolution after discontinuing them. EN appeared 1 week after taking fluvastatin, improved when stopped and reappeared after re-challenged.

Inflammatory bowel disease (ulcerative colitis and Crohn's disease) may also cause EN (34). It is relatively more frequent in ulcerative colitis (2 to 4%) than in Crohn's disease. EN is generally related with the activity of inflammatory bowel disease. Sometimes, EN may precede inflammatory bowel disease. The etiology was inflammatory bowel disease in three of our cases.

A standard treatment protocol for EN is lacking and it generally regresses spontaneously within 3 to 6 weeks (1, 2, 33). In most cases, bed-rest and wet compresses may suffice. The specific therapy is planned for the underlying disorder if any. For severe and recurring cases, non-steroidal anti-inflammatory drugs such as indomethacine 100-150 mg/day or naproxen 500 mg/day may be used. Saturated potassium iodine (5-15 drops/day in water or in orange juice, three times) or potassium iodine (400-900 mg/day) for 1 month is shown to relieve the nodosities for the unresolved cases. Systemic steroids, cholchicine, and hydroxychloroquine are rarely indicated. Our patients with EN who had non-infectious etiologies (19 cases) have been sent to the relative units. The ones who had infectious etiologies (21 cases) have been given specific treatment. We preferred naproxen (1000 mg/day, for 2 to 3 weeks) for the majority of our cases; they responded within 7 days. However, five patients did not respond completely to this drug given for 3 weeks and were switched to potassium iodine (900 mg/day). They responded within 7 days thereafter.

For our idiopathic EN cases, the nodosities in 2/3 of the patients recurred every year. These cases already had recurring lesions for years. It can be concluded that for the cases with recurring EN for years, an underlying etiology can not be found; and they are usually idiopathic. In the Lugo region of Northwestern Spain, relapses were also more common in patients with idiopathic EN than those with secondary EN. However among patients with secondary EN, they were found in those associated with nonstreptococcal upper respiratory tract infections or streptococcal infections (3).

Although not very frequent, EN is encountered all over the world and etiology description rests upon both medical knowledge and experience. Differentiating primary and secondary cases may be a challenge for the physician. Since there are plenty of probable etiologic causes, a wisely devised and cost-effective diagnosis is crucial. Generally, the etiology should be searched by a basic clinical approach (5).

Uncovering the etiology could not be posible in nearly half of the cases. Since the definite recognition of the etiology is challenging when a patient is admitted with EN for the first time, it is critical to know the factors predicting secondary EN. Among the five main EN series published in last 40 years (3, 4, 15-17), only one study (3) aimed to describe the variables favoring secondary EN. Among these, chest x-ray, history of non-streptococcal upper respiratory system infections, higher ASO level, tuberculin skin test, and the presence of synovitis and diarrhea were found to favor secondary EN. Clinical factors favoring secondary EN in our study are given in Table VII. Our study revealed that fever, leukocytosis, elevated CRP level, accelerated ESR, presence of cough, sore throat, diarrhea, arthritis,

and pulmonary pathology were predictors of secondary EN. Recurrence in EN significantly predicted primary EN. In conclusion, many disorders may lead to EN. Each center should determine its most frequent etiologies and thus devise a more practical approach to the patients with EN. This will shorten the time period for diagnosis and therefore will be more cost-effective.

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