Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2021;30:57-61
doi: 10.15570/actaapa.2021.14

Etiological factors and histopathological features in erythema nodosum: a 6-year retrospective cross-sectional study

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Abstract

Introduction: Erythema nodosum (EN) is the most common type of panniculitis. The most frequent etiological factors are streptococcal pharyngitis, sarcoidosis, Behçet's disease, and tuberculosis. Our objective was to identify the etiological factors and to evaluate the patients' clinical, laboratory, and histopathological findings.
Methods: Eighty-eight patients diagnosed with EN at our clinic between 2013 and 2019 were evaluated retrospectively. Sixty-five patients were evaluated histopathologically.
Results: The patients' ages ranged between 17 and 76 (mean age: 41.91 ± 13.07 years). EN was 7.8 times more frequent in women. Patients presenting with idiopathic EN were significantly older than secondary cases ($p < 0.05$). Sixty-one patients (69.3%) had an underlying disease (secondary EN). The most common etiological factors were upper respiratory tract infections ($n = 26$), followed by Behçet's disease ($n = 20$). Septal panniculitis was present in 89.2% of cases evaluated histopathologically. Mixed or lobular panniculitis was present in 35.7% of Behçet's disease patients with EN-like lesions. Vasculitis was also noted in 35.7% of Behçet's disease patients.
Conclusions: Our data confirm the predominance of upper respiratory tract infections and Behçet's disease among patients with EN in Turkey. Behçet's disease patients presenting with EN-like lesions may show mixed panniculitis and vasculitis, whereas classic EN patients predominantly show septal panniculitis.

Keywords: epidemiology, erythema nodosum, etiology, histopathological features, panniculitis

Received: 7 March 2021 | **Returned for modification:** 24 April 2021 | **Accepted:** 31 May 2021

Introduction

Erythema nodosum (EN) is the most common type of panniculitis, which develops as a reactive phenomenon against various stimuli (1). EN lesions are characterized by 1 to 10 cm erythematous and tender subcutaneous nodules located over the extensor aspects of the lower extremities that resolve in 3 to 6 weeks without leaving any scars or atrophy. EN is associated with a wide variety of stimuli such as infections, sarcoidosis, Behçet's disease (BD), rheumatologic diseases, inflammatory bowel diseases, medications, and pregnancy (1–3). The pathogenesis of EN is not fully understood. EN most probably results from immune complex deposition in and around the veins of the connective tissue septa of the subcutis (2, 3). Etiological factors show variability by geographical region (1, 4–7).

The objectives of this study are 1) to identify the etiological factors, 2) to evaluate the patients' clinical, demographic, laboratory, and histopathological features, and 3) to identify the differences between idiopathic EN and secondary EN.

Materials and methods

We reviewed the medical records of 88 patients that presented at the dermatology clinic at Cemil Taşcıoğlu City Hospital between 2013 and 2019. The diagnosis of EN was based on histopathological examination in 65 patients. In all cases, complete blood count, liver and renal function tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antistreptolysin O (ASO) level, urinalysis, pathergy test, throat swab for culture, and chest X-rays were investigated. In addition, depending on the clinical and/or laboratory findings, the following studies were carried out. A purified protein derivative (PPD) test was performed in 52 patients; this test was accepted as positive when an induration of > 10 mm was detected. An antinuclear antibody (ANA) test was performed in 28 patients, and a fecal occult blood test was ordered in the presence of diarrhea and abdominal pain. The diagnosis of streptococcal infection was established using two criteria: a high level of ASO (> 200 IU/ml) or the presence of *Streptococcus pyogenes* in the throat culture. EN was considered related to upper respiratory tract infection (URTI) if there was a history of URTI during the month before the onset of EN. The diagnosis of BD was established based on the criteria of the International Study Group (8), and sarcoidosis was diagnosed on the basis of clinical, radiological, and histopathological findings. Nodular lesions on the legs of patients that fulfilled the criteria for complete BD were considered EN–like lesions. Patients with nodular lesions due to superficial thrombophlebitis were excluded. EN was considered drug-induced if there was less than 1 month from the start of drug intake to the onset of EN. The recurrence of lesions after a disease-free period of at least 1 month was considered an attack. EN was classified as idiopathic (primary) or secondary to other diseases. The patients were considered to have idiopathic EN when no underlying diseases or precipitating events were found. The patients were considered to have secondary EN if the skin nodules occurred in association with a well-defined disease. The study protocol was approved by the Cemil Taşcıoğlu City Hospital ethical committee as protocol number 33.

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Statistical analysis

The statistical analyses were performed with the SPSS/PC software Statistics 22 (IBM SPSS, Turkey). Student's *t*-test was used for comparing parameters showing normal distribution, and the Mann–Whitney *U* test was used for comparing parameters that did not show normal distribution. Qualitative variables were analyzed with a chi-squared test and Fisher's exact test. In all the analyses, $p < 0.05$ was considered significant.

Results

The mean age of the patients with EN (Fig. 1) was 41.91 ± 13.07 years, ranging from 17 to 76, and 88.6% of the cases were female. The female-to-male ratio was 7.8 to one (78 females, 10 males). All of the cases associated with infections and sarcoidosis were female. Of the 20 BD patients, six were male; the female-to-male ratio was 2.3 in this group. Fourteen patients had concomitant systemic diseases.

In 27 patients (30.6%), no cause could be identified, whereas 61 cases (69.4%) had an associated disease (Table 1). The mean age of patients with idiopathic EN was significantly higher than that of patients with secondary EN ($p = 0.002$; Table 2).

The most frequent associations were URTI ($n = 26$) and BD ($n = 20$). These were followed by sarcoidosis, tuberculosis, urinary tract infection, pregnancy, granulomatous mastitis, and drugs (Table 1). Of the 26 cases associated with URTI in the previous month preceding the onset of EN, 22 had elevated ASO titers. The remaining four patients were classified as non-streptococcal URTI infections. *S. pyogenes* was isolated in only one patient.

Of the 20 patients with BD, all had oral aphthae, 10 had genital ulceration, eight had papulopustular lesions, three had uveitis, and three had vascular involvement. Pathergy positivity was present in eight patients (40%). Patients with BD presenting with EN-like lesions (Fig. 2) had significantly more attacks than other secondary cases ($p = 0.001$).

Of three patients with tuberculosis, two had pulmonary tuberculosis and one had tuberculous lymphadenitis. The diagnosis of pulmonary tuberculosis was established by chest X-ray and PPD testing upon presentation. The diagnosis of tuberculous lymphadenitis was verified by lymph node biopsy.

Patients with secondary EN had significantly elevated leukocyte, ASO, and ESR values when compared to those of idiopathic cases (Table 2).

Histopathological diagnosis was obtained in 65 patients. Septal panniculitis was detected in 58 patients (89.2%; Fig. 3), mixed (septal and lobular) panniculitis was noted in six patients (9.2%), and lobular panniculitis was detected in one patient (1.5%). Granuloma formation was present in 11 cases (17%). Of these 11 cases, four had sarcoidosis, three had idiopathic EN, two had tuberculosis, one had BD, and one had URTI. Biopsies were obtained from 14 patients with BD. Typical septal panniculitis was present in nine cases (64.3%), whereas mixed panniculitis was detected in four cases (28.6%; Fig. 4a, b) and lobular panniculitis was noted in one patient (7.1%). Vasculitis was present in five of 14 patients with BD (35.7%; Fig. 4c, d). Of the five cases with vasculitis, three had neutrophilic vasculitis and two had lymphocytic vasculitis.

Table 1 | **Etiological factors in our series.**

Factor	*n* (%)
Idiopathic	27 (30.7)
Secondary	61 (69.3)
URTI	26 (29.5)
BD	20 (22.7)
Sarcoidosis	6 (6.7)
Tuberculosis	3 (3.4)
Pregnancy	2 (2.2)
UTI	2 (2.2)
Drugs	1 (1.1)
Granulomatous mastitis	1 (1.1)
Total	88 (100.0)

URTI = upper respiratory tract infections, BD = Behçet's disease, UTI = urinary tract infections.

Table 2 | **Comparison of secondary and idiopathic erythema nodosum groups.**

	Secondary Mean ± *SD* (median)	Idiopathic Mean ± *SD* (median)	*p*
Age	39.08 ± 12.06	48.29 ± 12.56	0.002*
Leukocytes	8,682.62 ± 3,146.56 (7,800)	7,618.52 ± 3,745.19 (6,490)	0.031*
ESR	47.38 ± 34.31 (37)	28.93 ± 22.98 (18)	0.017*
ASO	325.41 ± 395.81 (181)	106.41 ± 58.06 (102)	0.002*
CRP	48.57 ± 64.99 (9)	12.56 ± 16.58 (6)	0.197
Number of attacks	3.46 ± 4.28 (1)	5.59 ± 5.92 (2)	0.095

ESR = erythrocyte sedimentation rate, ASO = antistreptolysin O, CRP = C-reactive protein, SD = standard deviation.
*p < 0.05.

Table 3 | **Comparison of our study with studies carried out in Turkey.**

Factors (%)	Mert et al., 2004	Mert et al., 2007	Adısen et al., 2007	Öz et al., 2010	Kısacık et al., 2013	Sula et al., 2015	Özbagcıvan et al., 2017	Öktem et al., 2017	This study 2019
Patients, *n*	50	100	72	66	107	33	81	287	88
Idiopathic	46	53	42	21	65	42	31	58	31
Secondary	54	47	58	78	35	58	69	42	69
URTI	16	11	23.6	9	8.4	21	23	16	29.5
BD	2	6	18	22	37.4	6	–	6	22.7
Sarcoidosis	12	10	1.3	15	16	3	7.4	2	6.7
TB	18	10	–	3	–	–	1.2	2	3.4
Drugs	–	5	4	19	–	12	2.5	2	1
Pregnancy	2	–	1.3	2	1.9	6	–	4	2.2
IBD	4	3	–	–	–	–	3.7	1	–
Malignancy	–	–	–	–	–	–	2.5	0.3	–
UTI	–	–	–	–	–	9	3.7	2	2.2
RD	–	–	–	6	1.9	–	13.5	5	–

URTI = upper respiratory tract infections, BD = Behçet's disease, TB = tuberculosis, IBD = inflammatory bowel disease, UTI = urinary tract infections, RD = rheumatological disease.

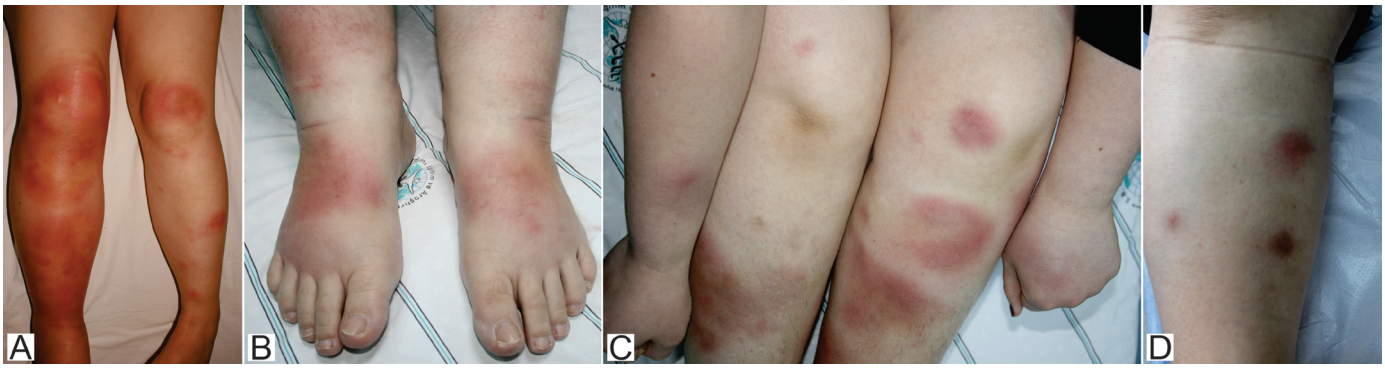

Figure 1 | Clinical features of erythema nodosum: (a) multiple oval slightly raised erythematous plaques and nodules, distributed bilaterally on the anterior aspect of the legs; (b) erythema nodosum involving the ankles; (c) widespread erythema nodosum distributed bilaterally on the anterior aspect of the legs, right arm, and left hand; (d) violaceous nodules located on the posterior aspect of the leg.

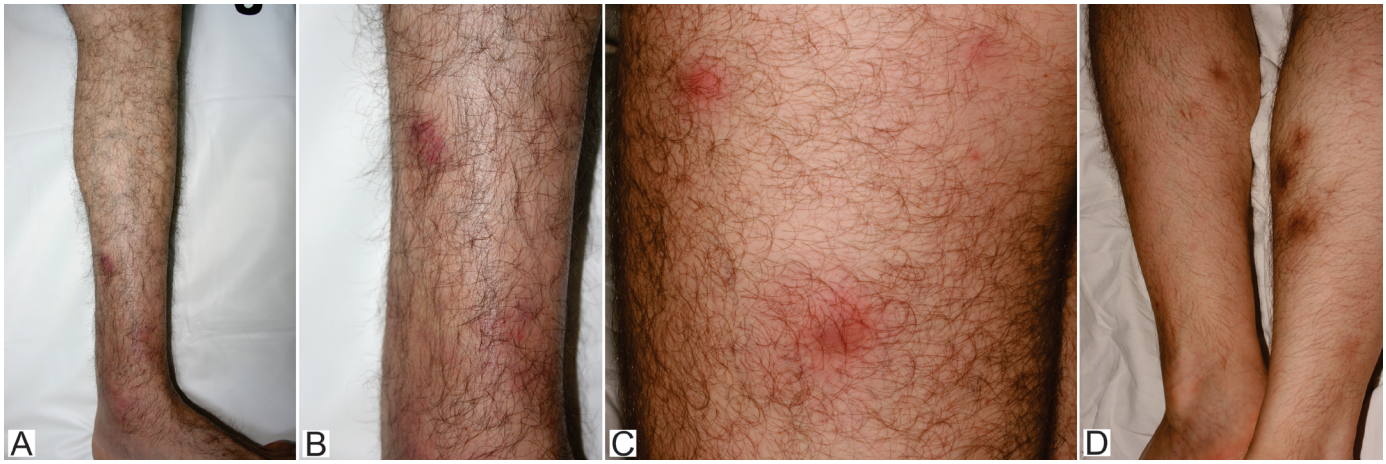

Figure 2 | Clinical features of erythema nodosum–like lesions: (a, b) nodular lesions located on the posterior aspect of the leg; (c) multiple erythematous nodules located on the femoral region; (d) erythema nodosum–like lesions resolving with post-inflammatory hyperpigmentation.

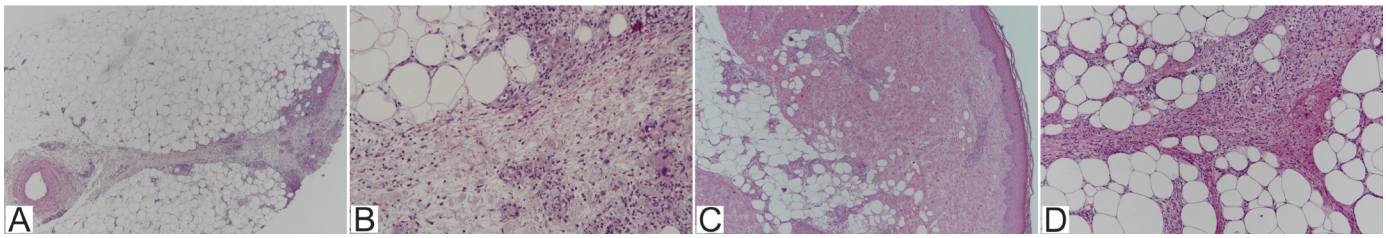

Figure 3 | Histopathological features of erythema nodosum: (a, b) scanning view showing a mostly septal panniculitis pattern; the inflammation is accompanied by multinuclear giant cells; (c, d) predominant septal panniculitis extending to the lobular area. H&E staining: (a) 40×, (b) 200×, (c) 40×, (d) 100×.

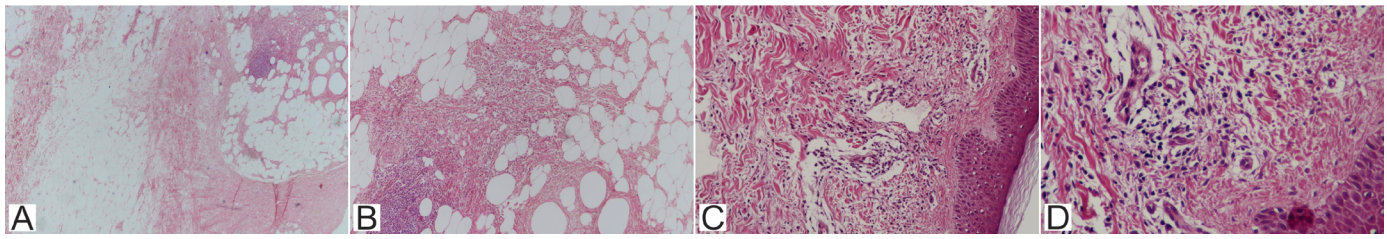

Figure 4 | Histopathological features of erythema nodosum–like lesions: (a, b) mixed panniculitis with dense infiltrate of neutrophils and mononuclear cells; (c, d) perivascular neutrophilic and lymphocytic infiltration and evidence of lymphocytic vasculitis. H&E staining: (a) 40×, (b) 100×, (c) 200×, (d) 400×.

Discussion

EN is the most common form of panniculitis developing as a reactive phenomenon due to various stimuli. Although the pathogenesis of EN remains unclarified, it is considered a delayed hypersensitivity response to a variety of antigenic stimuli, including bacteria, viruses, and chemical agents. Immune complexes may be deposited in the subcutaneous venules and adipose tissue septa (2); however, some authors have proposed a type IV reaction in the pathogenesis (3). Etiological factors are diverse and show variability with respect to geographical region (1, 4–7). This study examined the etiological, clinical, demographic, laboratory, and histopathological features of EN patients in our region.

EN developing after puberty is three to six times more frequent in women (1, 3, 4). On the other hand, the sex ratio is usually equal before puberty (9). We found a female-to-male ratio of 7.8 to 1 in our study. The female-to-male ratios were 2.42, 2.5, and 1.89 in the series by Adışen et al., Öz et al., and Kisacık et al., respectively (10–12). Öktem et al., Mert et al. (in two studies), and Sula et al. reported ratios of 5, 6, and 7.25, respectively (5, 13–15). We also

found a considerably high sex ratio in our series. Female predominance was less marked in patients presenting with EN-like lesions associated with BD because the female-to-male ratio was 2.3 in this subset. Kisacık et al. reported a female-to-male ratio of 1 in BD patients in their series (12).

The most common etiological factor was URTI (n = 26, 29.5%). In Turkey, nine studies were previously carried out on adult patients; the rates of URTI varied between 8.4 and 23.6% (Table 3) (5, 10–17). Of the 26 patients with URTIs, 22 had elevated ASO titers. Viral infections were considered the triggering factor in four patients with normal ASO titers, who had a history of URTI preceding the onset of EN. Streptococcal pharyngitis is a frequent cause of EN in both developed and developing countries (5, 14, 18–20). On the other hand, ASO titers may not be elevated in 20% of patients with streptococcal pharyngitis, whereas these patients may have increased levels of antistreptokinase and anti-DNAase (21). Accordingly, it is possible that some of the cases classified as idiopathic EN may have had streptococcal pharyngitis (18).

In our series, 22.7% of the patients had BD. This high rate is probably the result of a high prevalence of BD in Turkey and the presence of a follow-up clinic for BD patients at our hospital. In four studies performed at dermatology clinics in Turkey, the rates for BD were 18%, 22%, 6.3%, and 6% (10, 11, 13, 15). A recent study carried out at a rheumatology clinic in Turkey showed a high rate of 37.4% (12). However, the rates of BD were lower (2–6%) in Mert et al.'s three studies (5, 14, 16); this may be explained by the fact that these studies were carried out at an infectious disease clinic. The rates for BD were considerably lower in studies performed outside Turkey (Table 4) (4, 6, 7, 18–20). Patients with BD presenting with EN-like lesions had more frequent relapses; this is consistent with the finding by Adışen et al. (10).

EN is the most common nonspecific skin manifestation of sarcoidosis (22). Sarcoidosis is a frequently encountered etiological factor in European countries (Table 4) (4, 6, 18, 22). Its prevalence is very low in the Middle East and South Asia (7, 19). The rates reported from European countries vary between 5.6 and 28% in various series (Table 4) (4, 6, 18, 20). The rates for sarcoidosis varied between 1.3 and 15.9% in studies reported from Turkey (Table 3) (5, 9–17), whereas in our series, 6.7% of the patients had sarcoidosis. The prevalence of sarcoidosis in Turkey is unknown (16), but it is possible that it is between the prevalence rates in Europe and Asia.

Tuberculosis is the causative agent in 2 to 20% of cases with EN (11). The rates for tuberculosis varied between 0 and 18% in previous studies from Turkey (Table 3) (5, 9–17), whereas reports from Europe showed rates between 1 and 7% (Table 4) (4, 6, 18, 20). A recent report from Chile showed a rate of 6.6% (23). Tuberculosis was present in 3.4% of our series. Of all tuberculosis cases, primary tuberculosis is the most common cause of EN (5, 12, 14). Nevertheless, one of our cases was diagnosed as tuberculous lymphadenitis.

Both pregnancy and oral contraceptive administration have been associated with EN (1, 2). In our series, two patients (2.3%) had pregnancy-induced EN. One of the patients had EN during the second trimester and the other one developed EN 2 days following delivery. Because there were no other etiological factors and given the close temporal association, the second patient was also considered to have pregnancy-associated EN.

Urinary tract infections may rarely be an etiologic factor in EN. Urinary tract infections were not found to be a causative factor in the literature except in three studies reported from Turkey (13, 15, 17).

Drugs may precipitate EN in less than 20% of cases (11). Most commonly, oral contraceptives, sulphonamides, amoxicillin, and proton pump inhibitors may cause EN (1, 10). In our series, there was one drug-induced case probably caused by ciprofloxacin, but it is very difficult to elucidate the correct etiological factor in situations when an antibiotic is taken because EN may also be triggered by the infectious process.

EN may rarely be associated with idiopathic granulomatous mastitis (24). In our case, the diagnosis of granulomatous mastitis was verified by histopathologic examination.

When idiopathic and secondary cases were compared, younger age, leukocytosis, and increased ESR and ASO values were found to be predictors of secondary EN (Table 2). This finding was consistent with the results of Mert et al. and Kısacık et al. (5, 12, 14). Patients with idiopathic EN were older than those with secondary EN; this finding was consistent with the results of several studies (5, 10, 11–14, 16, 18, 23). We could not find any significant difference between idiopathic and secondary cases with respect to the number of attacks, whereas Adışen et al. reported that secondary cases relapsed more frequently (10). Conversely, Mert et al. stated that idiopathic cases relapsed more frequently (5, 14, 16).

The large majority of patients associated with infections, sarcoidosis, drugs, or pregnancy as well as idiopathic cases showed typical septal panniculitis, but mixed or lobular panniculitis and vasculitis were noted in 35.7% of patients with BD that presented with EN-like lesions. Demirkesen et al. and Yi et al. reported that septal panniculitis, lymphocyte-predominant infiltrate, and absence of vasculitis were features of EN, whereas mixed or mostly lobular panniculitis was observed in the EN-like lesions in more than 85% of cases (25, 26). Misago et al., on the other hand, reported that septal panniculitis was present in 50% of their 26 cases with BD, and mixed panniculitis in 50%; they found a rate of 73% for vasculitis (27). In the study by Demirkesen et al., inflammation

Table 4 | Comparison of our study with studies carried out in Europe, Asia, and South America.

Factors (%)	Spain 1983	Israel 1987	Spain 1991	France 1998	Singapore 2000	Spain 2000	Greece 2000	Chile 2017	This study 2019
Patients, *n*	160	50	68	129	75	106	72	91	88
Idiopathic	32	32	46	55	60	37	35	31	31
Secondary	68	68	54	45	40	63	65	69	69
URTI	16	44	24	28	9	8	12	32	29.5
BD	1	–	–	–	3	2	4	2.2	23
Sarcoidosis	21	2	7	11	–	20	28	11	6.7
TB	6	2	7	1	3	5	2	6.6	3.4
Drugs	18	10	6	–	–	3	7	1	1
Pregnancy	2	–	–	–	4	–	6	–	2
IBD	1	–	3	2	–	2	–	2	–
Malignancy	1	–	–	–	–	1	–	–	–
UTI	–	–	–	–	–	–	–	–	2

URTI = upper respiratory tract infections, BD =Behçet's disease, TB = tuberculosis, IBD = inflammatory bowel disease, UTI = urinary tract infections.

of the vessel wall was noted in 72.9% of 24 BD cases, and 60% of these cases had neutrophilic vasculitis (25). Lymphocytic vasculitis was present in 60% and neutrophilic vasculitis was noted in 28% (totaling 88%) of 25 patients in Yi et al.'s study (26). The presence of neutrophilic or lymphocytic vasculitis might be related to the evolution of EN-like lesions (28). Our lower rates for mixed/lobular panniculitis and vasculitis are probably the result of the small number of cases.

Granulomatous panniculitis was more frequent in patients presenting with sarcoidosis and tuberculosis in our study. Miescher's radial granulomas, which are nodular aggregations of small histiocytes around a central cleft, are present in the early and late stages of the evolution of EN lesions (1, 26). We could not find any literature reporting the predominance of granulomatous panniculitis in granulomatous disorders.

Limitations

Because the data were evaluated retrospectively, some data could have been recorded incorrectly. An ASO titer was ordered once, and serial evaluations were not performed; in addition, infections with *Mycoplasma pneumoniae*, EBV, and CMV were not evaluated. Because EN is a multifactorial disorder, some cases may have had more than one etiological factor. In such cases, it is very difficult to identify the correct etiological factor.

Conclusions

URTIs and BD were the predominant etiological factors in our study. It is evident that the etiology of EN varies by the department where the patients are treated. Younger age, leukocytosis, and increased ESR and ASO values were found to be predictors of secondary EN. BD patients presenting with EN-like lesions may have more frequent relapses, and female predominance is probably less marked in this group. The majority of patients showed typical septal panniculitis. However, mixed panniculitis and neutrophilic or lymphocytic vasculitis may be observed in BD patients with EN-like lesions.

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