

Erythema nodosum: A clinical approach

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Erythema nodosum (EN) is the most common cause of inflammatory nodules, occurring usually on the lower extremities. It is generally considered a benign and self-limiting hypersensitivity reaction characterized by multiple and bilateral non-ulcerating lesions (Fig. 1). These gradually evolve from painful inflammatory, non-scarring cutaneous and subcutaneous red nodules to a bruised appearance and complete resolution (1-3).

In patients with EN a skin biopsy of the subcutaneous nodules shows acute or granulomatous septal panniculitis with primary inflammation around the veins of the septal system, constituted of neutrophils, lymphoid cells, and histiocytes, with or without giant cell formation adopting occasionally a granulomatous inflammatory infiltrate that typically spare the fat lobules except by contiguous spread.

Erythema nodosum may be idiopathic or associated with a wide spectrum of conditions including systemic diseases, infections, treatment with various drugs, pregnancy, and exceptionally with malignancies (1-6). The prognosis of the skin lesions is usually excellent, but the presence of possible underlying conditions needs to be excluded (4, 7). There are no specific indicators to raise the suspicion of the possible presence of an underlying condition associated with EN. For these reasons several points can be made regarding the diagnosis of this condition:

- 1) In the presence of typical clinical manifestations, EN can be diagnosed in a straightforward fashion by expert clinicians who often see this condition. A skin biopsy, however, is required to confirm the presence of the disease and to avoid a misdiagnosis of other entities presenting with subcutaneous nodules such as nodular vasculitis, cutaneous polyarteritis nodosa, or even other conditions such as erythema induratum of Bazin or subcutaneous lymphoma.
- 2) In series of patients with EN, an association with other diseases has been observed in more than 60% of cases.
- 3) Erythema nodosum limited to skin is remarkably predictable in its rapid and sometimes complete improvement after bed-rest and, in some cases, with non-

steroid anti-inflammatory drugs or low-dose prednisone therapy (7).

4) In a typical case, an extensive work-up for underlying conditions is not needed.

5) Nevertheless, in view of the lack of specific diagnostic tests the clinician should remain alert to the possibility of a disease presenting with EN, and clues to the presence of another disease should be considered seriously.

The actual proportion of patients with EN is not well defined and underlying conditions may vary in different populations. In the Lugo region of North-western Spain, where there is a single reference hospital for systemic diseases (8), between 1988 and 1997 the annual incidence rate of biopsy-proven EN for the population 14 years and older was of 52 cases/million; men 24 cases/million, women 79 cases/million (7).

Erythema nodosum has been associated with a wide and diverse spectrum of conditions. In Table I the causes of EN are shown. Idiopathic EN, however, is not uncommon; it accounted for 37% of the cases in Northwest Spain (7). In another recent study from Greece the cause of EN was not found in 35% of the cases (9). In Northwest Spain, idiopathic EN was more common in women, with a predominant distribution of disease onset during the winter and



Fig. 1. Typical lesions of erythema nodosum.

Table I. Main conditions associated with erythema nodosum.

Infections	Streptococcus beta hemolyticus infection
	Primary tuberculosis
Systemic diseases	Yersinia, salmonella, and campylobacter infections
	Other infections: toxoplasmosis, blastomycosis, histoplasmosis, primary coccidioidomycosis, syphilis, leprosy, invasive amebiasis and giardiasis, brucellosis, hepatitis B virus infection, infectious mononucleosis, cytomegalovirus and mycoplasma infections
Malignancies	Sarcoidosis
	Inflammatory bowel disease (ulcerative colitis and Crohn's disease)
Medications	Behçet's disease
	Connective tissue diseases
Pregnancy	Sweet's syndrome
	Hematologic neoplasms (in particular, lymphomas)
Solid tumors (very uncommon)	Oral contraceptives
	Penicillins
Others	Bromides
	Iodides
Analgesics	Analgesics
	Others

spring months (7). Relapses were often observed within the first year after the diagnosis. In that study only 1 of the 35 patients initially diagnosed as having idiopathic EN who were followed for at least one year was finally diagnosed as having a well-defined underlying condition associated with the subcutaneous nodules (7).

Among the underlying conditions associated with EN, included within the group of secondary EN, streptococcal pharyngitis or non-streptococcal upper respiratory tract infections (URTI) constitute common precipitating events that may be implicated in the occurrence of the cutaneous lesions (9). Infectious diseases such tuberculosis, yersinia, salmonella, and campylobacter infections, and less frequently others such as toxoplasmosis, blastomycosis, histoplasmosis, primary coccidioidomycosis, syphilis, leprosy, invasive amebiasis and giardiasis, or even brucellosis should be considered in the context of a specific epidemiologic background in different regions of the world (7). Thus, geographic peculiarities are certainly implicated in the characteristic spectrum of EN. More rarely, other infections have also been reported to be associated with EN (Table I). Acute sarcoidosis often presents with constitutional symptoms, arthritis (especially in the ankles), or periarticular

ankle inflammation and EN (10). The diagnosis of sarcoidosis should be based on a tissue biopsy, but a patient with typical Löfgren's syndrome, frequently associated with bilateral hilar or right paratracheal lymphadenopathy, may not require biopsy proof. In our experience, serum angiotensin-converting enzyme can be used for monitoring disease activity in the follow-up of patients, but because of a lack of sensitivity and specificity its diagnostic value is low (7). In addition, other entities such as chronic inflammatory bowel disease, Behçet's disease, connective tissue diseases or Sweet's syndrome, and solid and especially hematologic malignancies have been observed to be associated with EN (7, 9, 11). Drugs (such as antibiotics, non-steroid anti-inflammatory drugs, analgesics and oral contraceptives) and pregnancy have also been implicated in the occurrence of this condition (7, 9, 12).

An important concern for the clinician is to discriminate between patients with EN associated with a well-defined and potentially treatable condition, and those considered as being idiopathic. Since the list of possible etiologic factors of EN is extensive, a rational cost-effective diagnostic approach in patients with EN is desirable.

In view of the above, we would suggest the following diagnostic approach in

patients presenting with acute inflammatory subcutaneous nodules on the lower extremities (Fig. 2A). We also propose a work-up to be performed in patients with cutaneous lesions consistent with EN (Fig. 2B).

A) A clinical history should be taken, and the interview should include:

1. Duration of symptoms, with special reference to previous episodes of cutaneous nodules.
2. Previous history of drug intake, including contraceptives, which may be responsible for the development of EN.
3. A recent history of pregnancy.
4. Data about possible infections, such as pharyngitis or tonsillitis that may suggest a previous streptococcal infection or any viral non-streptococcal URTI, which may be the precipitating event for the subcutaneous nodules.
5. A history of diarrhea, which may suggest an underlying inflammatory disease or intestinal infection.
6. Exclusion of symptoms of connective tissue diseases or the antecedent of oral and genital ulcers and uveitis, which may suggest the presence of EN associated with Behçet's disease.

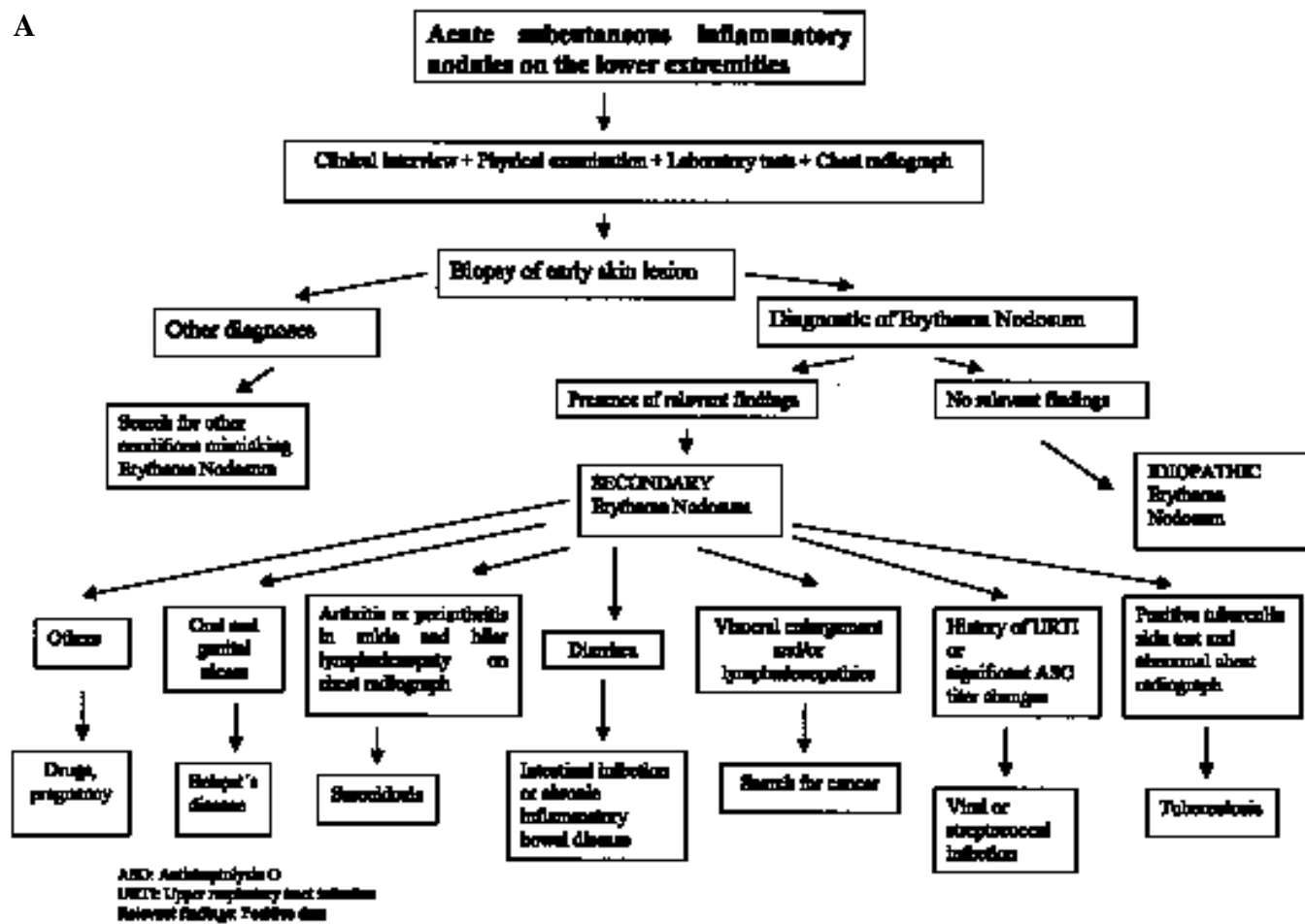
B) Physical examination:

1. Presence of arthritis or periarticular ankle inflammation should require the search for acute sarcoidosis.
2. Presence of oral and genital ulcers may be an indication for Behçet's disease in countries where this condition is common.
3. Although uncommonly associated, the presence of visceral enlargement or lymphadenopathies should require a search for either solid or hematologic malignancies, in particular non-Hodgkin lymphomas.

C) Skin biopsy of the nodules should always be undertaken to confirm the presence of EN, which is pathologically defined as a septal panniculitis, and to exclude other conditions presenting with subcutaneous nodules and mimicking this condition. Early biopsy of the inflammatory lesions is advisable, as lesions in resolution may yield non-specific pathologic findings.

D) Laboratory analysis should include full blood counts and a routine biochemistry profile including liver and

A



(B)

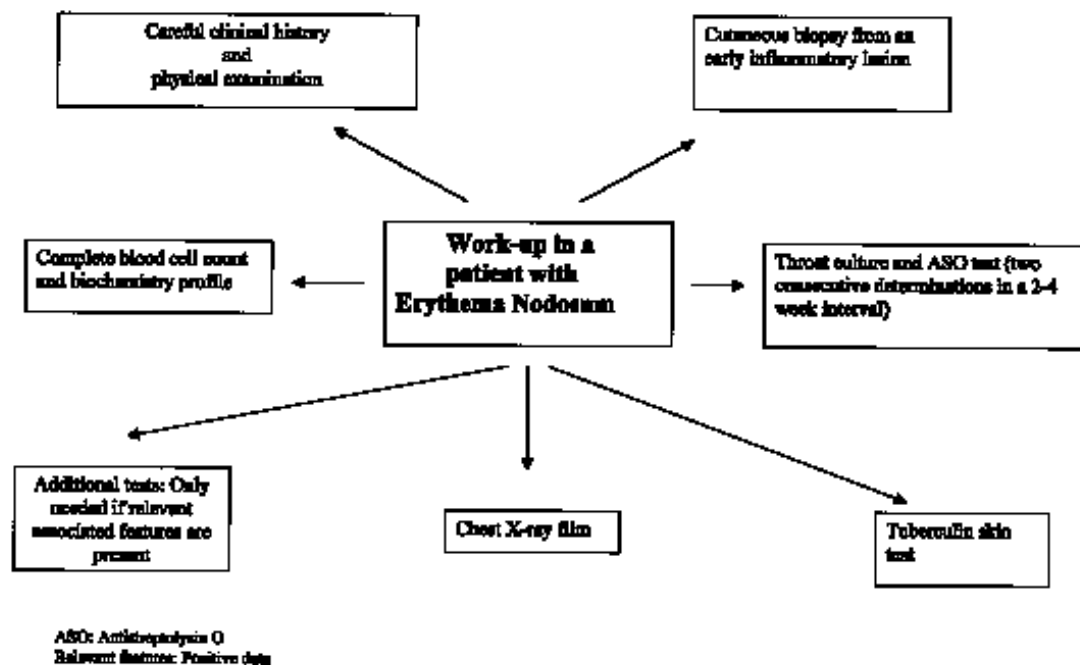


Fig. 1. (A) Diagnostic approach in patient presenting with subcutaneous nodules. (B) Proposed work-up in a patient with cutaneous lesions consistent with erythema nodosum.

renal function tests. The presence of unexplained anemia may be associated with a silent chronic inflammatory bowel disease. Moreover, throat culture and in particular 2 consecutive determinations of antistreptolysin O (ASO) should be performed in a 2- to 4-week interval (to be considered positive if there is a significant change in the ASO titer of at least 30%).

E) Chest radiograph should also be routinely performed as EN may be the presenting manifestation of sarcoidosis or tuberculous.

F) Tuberculin skin test. Although in areas where tuberculosis is relatively common a tuberculin test does not always imply the presence of active tuberculosis, an intradermal tuberculin test is important in the diagnosis of EN, as it may be the first clue to the presence of an underlying tuberculosis.

In summary, although EN is generally a benign and self-limited condition, it may be associated with a wide spectrum of diseases. To assess the best approach and reduce morbidity and the

cost of diagnosis, its management should include a detailed clinical history and physical examination, with a systematic search for possible associations with sarcoidosis and certain infectious diseases such as tuberculosis or streptococcal infections. Additional studies are usually not informative and should only be performed in cases presenting relevant associated clinical features. When none of these specific features are found, the presence of an underlying disease associated with EN is unlikely. However, geographic peculiarities may cause differences in the clinical spectrum of the disease. Thus, these peculiarities may make it advisable to follow specific recommendations for the evaluation of particular conditions associated with EN in each region.

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