Erythema Nodosum — Differential Diagnosis and Treatment

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Erythema nodosum (EN) is a reactive process of the skin which can be triggered by a number of factors. EN is an acute, but self-limiting disease with preponderance for females in 20 to 40 years of age. In this article, epidemiology, etiology, pathophysiology, symptoms, diagnosis, differential diagnosis and therapy of EN will be discussed.

Definition and Epidemiology of Erythema Nodosum

EN is a type of panniculitis (most common), which is characterized by a sudden onset of red, warm, and tender nodular eruptions on shins. Erythema nodosum may be accompanied by other symptoms such as fever. A number of factors can trigger EN; hence, it is supposed to be a cutaneous reactive process.

Incidence and prevalence

Incidence and prevalence of EN varies with varying etiological factors and geographical locations. Studies from Spain have shown the average annual incidence of biopsy proven
EN in patients aged 14 years and above to be 52 cases per million population. The prevalence of EN in a study from a semi-rural area of England was 2.4 cases per thousand population per year.

Age
EN is known to occur at all ages; however, maximum numbers of cases are between second and fourth decades of life. A high incidence has been seen between 20 and 30 years of age. This could be due to the high incidence of sarcoidosis in this age group which is associated with EN.

Sex
EN is seen to occur more in women than men, with the occurrence being three to six times more in women. However, in the prepubertal age groups, the incidence is the same among girls and boys.

Associated diseases
EN is known to be associated with the following diseases in 15 – 30% of cases:

- Sarcoidosis
- Sweet’s syndrome
- Throat infection
- Acute myelogenous leukemia
- Crohn’s disease

Etiology of Erythema Nodosum
A number of etiological factors have been implicated to trigger EN:

Bacterial infections: The most common ones are tuberculosis, streptococcal infections, brucellosis, atypical mycobacterial infections, Q fever, mycoplasma pneumoniae infections, rickettsiae, salmonella infection, shigella infection, yersinia and chlamydia psittaci.

Viral infections: Hepatitis B, hepatitis C, infectious mononucleosis, etc.

Fungal infections: Aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, sporotrichosis, etc.

Protozoal infections: Ascariasis, giardiasis, toxoplasmosis, etc.

Drugs: A number of drugs are known to trigger EN. The most commonly implicated are acetaminophen, amoxicillin, bromides, carbamazepine, cotrimoxazole, dicloxacillin, diethylstilboestrol, furosemide, granulocyte colony stimulating factor, ibuprofen, infliximab, levofloxacin, medroxyprogesterone, minocycline, naproxen, oral contraceptives, penicillin, phenytoin, verapamil, progestins, propylthiouracil, sulfamethoxazole, sulfonamides, sulfasalazine, and trimethoprim.

Malignant diseases: EN has not been very well documented with malignancies; however, few reports show an association with adenocarcinoma of colon, carcinoid tumor and carcinoma of uterine cervix.

Other diseases: Acne fulminans, Adult-onset Still’s disease (AOSD), ankylosing
spondylitis, behcet disease, celiac disease, Crohn’s disease, IgA nephropathy, intestinal bypass syndrome, Lupus erythematosus, pregnancy, relapsing polychondritis, reactive arthritis, sarcoidosis, Sjogren’s syndrome, sweet’s syndrome, ulcerative colitis, and granulomatosis with polyangiitis.

**Streptococcal infection of upper respiratory tract**: Group A beta-hemolytic streptococcal infection is followed by EN 2 to 3 weeks later. It is a common trigger for EN among children and young adults. ASO titres are elevated; however, the throat cultures are negative.

**Tuberculosis**: EN triggered by tuberculosis is seen in areas with a high prevalence of tuberculosis. It is seen in children with primary pulmonary infection.

**Sarcoidosis** is an important trigger for EN among adults.

**Lofgren’s syndrome** seen in sarcoidosis is characterized by EN, hilar adenopathy and arthritis around the ankles.

**Inflammatory bowel disease (IBD)** is associated with EN in adults and precedes bowel symptoms. **Crohn’s disease** is more frequently associated with EN than **ulcerative colitis**.

In 37% to 60% of cases, the etiology of EN cannot be determined.

### Pathology and Pathophysiology Erythema Nodosum

The pathogenesis of EN is not well understood. Some studies have shown the following:

**Cutaneous reactive process**: EN can be triggered by a number of diverse factors; hence, it has been proposed to be a cutaneous reactive process. A few studies have demonstrated the deposition of immune complexes in the subcutis. To support this, a few studies have demonstrated circulating immune complexes, complement activation and deposition of immunoglobulins in the subcutaneous fat septa. Other studies have proposed **type IV hypersensitivity** as a possible pathogenetic mechanism.

**Reactive oxygen intermediates (ROI)**: Patients have activated neutrophils in peripheral blood, and they produce ROI, which is four times higher as compared to healthy people; hence, ROI have been proposed to cause oxidative tissue damage and tissue inflammation.

**Genomic anomaly**: A genomic anomaly in the human TNF-alpha gene promoter where nucleotides exchange (G-A) is seen at position-308. This leads to the secretion of an uncommon TNF alfa II. This is seen in sarcoidosis associated EN patients. In a few EN patients, a polymorphism of macrophage MIF gene takes place at position-173, which is associated with an increased risk for developing sarcoidosis.

**Increased proinflammatory cytokines**: Raised levels of serum IL-6 has been seen in EN due to infectious and non-infectious causes. Skin lesions and peripheral blood of EN patients have shown increased levels of Th1 cytokines (IL-2 and IFN-gamma).

### Symptoms of Erythema Nodosum

EN is characterized by a sudden development of nodules on the skin, which may be
accompanied by fever (38 – 39 ºC), cough, joint pains, malaise, abdominal pains, vomiting, diarrhea and headache.

The characteristic lesions of EN are nodules which are _erythematous, warm and painful to touch_. The nodules may vary in size from 1 to 5 cm or more in diameter. Nodules may often merge to form _erythematous plaques_.

They involve the body symmetrically and bilaterally with a predilection for _shins, ankles and knees_, but may involve other sites such as thighs, face, neck and extensor parts of arms. The nodules/plaques change in color with time i.e. bright red and elevated (early lesions) then livid red/purple and flat; finally a yellow or greenish appearance. As color change mimics that of a deep bruise, hence they were also known as _erythema contusiformis_. The lesions stay for 3 – 6 weeks and subside without marks or scarring; however, recurrences of EN are common.

_Eye manifestations_ in the form of episcleral lesions and phlyctenular conjunctivitis have been seen with skin lesions.

_Splenomegaly, hepatomegaly, lymphadenopathy_ and _pleuritis_ have been rarely seen among EN patients.

**EN in children** has a shorter duration with less frequent occurrence of fever and arthralgias as compared to adults.

## Diagnosis of Erythema Nodosum

The clinical history and relevant investigations should be done to find the trigger factors for EN; however, a _skin biopsy_ is essential to make a confirmatory diagnosis of EN.

- **Clinical history** is a must and should include a detailed history about past diseases, medications, pets, hobbies, travel history and any familial cases.
- **Blood investigations**: Complete blood count, ASO titre and erythrocyte sedimentation rate.
- **Urinalysis**.
- **Throat culture**.
- **Intradermal tuberculin test, chest X-ray** should be preferred to rule out tuberculosis. In places where tuberculosis is endemic, _IFN gamma release assay_ should be used as tuberculin test will be positive in most adults.
- Specific serological tests may have to be done for bacterial, viral, fungal and protozoal infections prevalent in an area.
- **Skin biopsy**: Histopathology of EN shows a _septal panniculitis without vasculitis_. An inflammation and edema of connective tissue septa is observed. The inflammatory cell infiltrates vary from neutrophils in early lesions of EN to lymphocytes and histiocytes in later stages.

The most characteristic feature of EN histopathology is _Miescher’s radial granulomas_. These are small, nodular aggregates of _histiocytic cells_ around a central stellate or banana shaped cleft. These are found in the subcutis. The older lesions of EN may show the histiocytic cells grouping to form multinucleated giant cells.

## Differential Diagnosis

- Patients with _Behcet’s disease_ may also present with EN-like lesions which are histopathologically different than the EN lesions.
Therapy of Erythema Nodosum

Identification and management of underlying etiology is essential as a number of factors may underlie an episode of EN. Besides managing the underlying cause, the following treatment is given specifically for EN:

- **Bed rest** and limiting physical exercise.
- **Relieving pain and to quicken recovery**: Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and naproxen.
- **Potassium iodide**: Resistant cases of EN have been treated with potassium iodide, but severe hypothyroidism may occur as a side effect of potassium iodide.
- **Steroids**: Systemic steroids should be avoided in EN patients as an underlying infectious etiology may flare up. It is administered only in cases of non-infectious etiology not responding to other therapies.
- **Other drugs**: Other medications which have a sore throat with success are colchicine, hydroxychloroquine and anti-TNF drugs (etanercept, infliximab and adalimumab).

Progression and Prognosis of Erythema Nodosum

EN is **self-limiting** and regresses on its own in 3 to 4 weeks. However, **relapses** are frequent and more often seen in cases of EN, which are idiopathic or associated with streptococcal upper respiratory tract infections.

Rare complications seen with EN are **retrobulbar optic neuritis**, EN coexisting with **erythema multiforme**, EN coexisting with **lichen planus** and EN with concomitant reactivation of hepatitis C viral infection.

Important points to remember

- EN is the most common panniculitis.
- EN affects women more in age group between 20 and 40 years.
- Most common etiological factors associated with EN are sarcoidosis, tuberculosis and streptococcal throat infections.
- EN presents as acute bouts of nodules on shins, which are painful and red and changes color with time.
- Characteristic histopathological feature of EN is Miescher’s granuloma.

Review Questions

The correct answers can be found below the references.

1. Lofgren’s syndrome is characterized by which the following?
   - A. Erythema nodosum, hilar lymphadenopathy, arthritis around ankles.
   - B. Erythema nodosum, generalized lymphadenopathy.
C. Erythema multiforme, elevated ESR and conjunctivitis.
D. Acute urticaria, fever and lymphadenopathy.

2. An 18-year-old male presents with erythematous, tender eruptions on shins since one day. She gives a history of sore throat 2 weeks back. What is the possible diagnosis?
   A. Acute urticaria.
   B. Erythema multiforme.
   C. Erythema nodosum.
   D. Rheumatic fever.

3. A 25-year-old woman of African origin with a history of sarcoidosis presents with tender, red eruptions on her lower legs. A skin biopsy of the lesions would show which of the following?
   A. Septal panniculitis with vasculitis with eosinophil infiltrates.
   B. Miescher’s radial granuloma with septal panniculitis.
   C. Abundant lymphocytes in dermis with a clear subcutis.
   D. Inflammatory cells, mainly neutrophils seen in epidermis and no involvement of dermis and subcutis.

References

Erythema Nodosum Differential Diagnoses via medscape.com

Correct answers: 1A, 2C, 3B

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