

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 vary 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, the maximum number of cases is between the **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 the colon, carcinoid tumor and carcinoma of the 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 the 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 titers 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 °C), **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 of past diseases, medications, pets, hobbies, travel history, and any familial cases.
- **Blood investigations:** complete blood count, ASO titer 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 a 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 **septal panniculitis without vasculitis**. Inflammation and edema of connective tissue septa are 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.

- Acute urticaria
- Erysipelas
- Erythema induratum (Nodular vasculitis)
- Insect bites
- Superficial thrombophlebitis

Therapy of Erythema Nodosum

Identification and management of underlying etiology are 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 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 that 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 the age group between 20 and 40 years.
- The 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.**

References

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