Erythema Nodosum

Erythema nodosum is presumed to be a hypersensitivity reaction. It is often a dermatological manifestation of infectious, or other, disease.[1]

Epidemiology

The prevalence varies from country to country. It is most prevalent in women in their 20s to 30s.[2] It has a prevalence of 2.4 per 10,000.[3]

Presentation[4]

The eruptive phase begins with fever, aching and arthralgia whilst a painful rash usually appears within a couple of days.

Lesions begin as red, tender nodules. The borders are poorly defined and they are 2-6 cms in diameter.

In the first week the lesions become tense, hard and painful. In the second week, they may become fluctuant, rather like an abscess but they do not suppurate or ulcerate. Individual lesions last around two weeks but occasionally, new lesions continue to appear for three to six weeks.

Aching legs and swollen ankles may persist for many weeks. In the first week they are bright red but in the second week there is a blue or purple hue, even turning yellow like a resolving bruise before disappearing in a couple of weeks.

They can occur anywhere but are usually on the anterior aspect of the lower leg.

When the aetiology is an infection the lesions usually heal in six to eight weeks but 30% of idiopathic cases last six months. Arthralgia occurs in more than half of patients and begins either during the eruptive phase or two to four weeks before. Joints are red, swollen and tender; sometimes with effusions. Morning stiffness may occur. The ankles, knees and wrists are most often involved. Synovitis resolves in a few weeks but joint pain and stiffness may last up to six months. There are no destructive changes in the joint and synovial fluid is acellular and the rheumatoid factor is negative.
Associated diseases and causes

- Erythema nodosum is often indicative of an underlying infectious disease but a cause is not always found. Some underlying causes are not infectious.
- Streptococcal infection is the most common underlying cause and so it may be a feature of other diseases, including scarlet fever and rheumatic fever, although in the UK nowadays the former is uncommon and the latter rare.
- Sarcoïdosis is also commonly involved in adults, although it is not infectious in origin.
- Tuberculosis must be considered.
- Leprosy can produce a clinical picture of erythema nodosum, although the histological picture of the lesions is different.
- Various forms of gastroenteritis - especially *Yersinia enterocolitica*, *Salmonella* spp. and *Campylobacter* spp. - can be associated.
- Lymphogranuloma venereum may be a cause.
- Mycoplasma pneumonia can be associated.
- Fungal infections are less common in the UK but coccidioidomycosis is important in Southwest USA. It may occur in histoplasmosis and blastomycosis.
- Sulfonamides are used less often nowadays but other drugs to be implicated include sulfonylureas, gold and oral contraceptives.
- It may correlate with flare-up of Crohn's disease or ulcerative colitis.
- It can precede the diagnosis of Hodgkin's lymphoma and non-Hodgkin's lymphoma by months and it can accompany Behçet's syndrome.
- It may occur in pregnancy when it is usually in the second trimester. It is likely to recur in future pregnancies and may occur with oral contraceptives.
- There are rare cases (<1 in 100) associated with Epstein-Barr virus, hepatitis B and hepatitis C and HIV.
- In many cases no cause is found.

Investigations

Although in many cases it is idiopathic, it is important to exclude serious underlying disease:

- A throat swab for streptococcus is the first test, although it may well be negative, even with streptococcal disease.
- Anti-streptococcal O (ASO) titre may be more helpful, although a normal titre does not exclude infection. A rising titre may be more valuable.
- Arrange an FBC and ESR. ESR is often very high regardless of the aetiology, and CRP may be more contributory.
- Stool examination for *Y. enterocolitica*, *Salmonella* spp. and *Campylobacter* spp. may yield results, as may blood cultures.
- In sarcoïdosis, calcium and angiotensin-converting enzyme (ACE) are often raised.
- CXR may show bilateral hilar lymphadenopathy (BHL) in sarcoïdosis, unilateral or asymmetrical adenopathy in malignancy, or evidence of pulmonary tuberculosis.
- Intradermal skin tests may be required to exclude tuberculosis and coccidioidomycosis.
- Excisional biopsy may be helpful where the diagnosis is in doubt.

Differential diagnosis

- *Erysipelas*.
- *Erythema induratum* (modular vasculitis).
- *Insect bites*.
- *Acute urticaria*.
- *Familial Mediterranean fever*.
- *Superficial thrombophlebitis* (standard or superficial migratory thrombophlebitis).
Management

- Most cases are self-limiting and require only symptomatic relief.
- If an infective aetiology has been discovered then appropriate therapy is in order but it should not be given blind.
- A degree of relief can be obtained with cool compresses and bed rest with elevation of the foot of the bed. Bed rest has been advocated for many years and is anecdotally useful but the evidence base is lacking.
- Non-steroidal anti-inflammatory drugs (NSAIDs) are useful and no other drugs are usually needed. Steroids are beneficial but should be used with caution and may be contra-indicated if infection has not been excluded.
- In difficult cases, oral potassium iodide may be valuable, as may tetracycline and, in erythema nodosum of leprosy, thalidomide has seen a resurgence but further research is required.\textsuperscript{10, 11, 12}

Prognosis

The condition usually resolves within six weeks but it may be more protracted, especially if the underlying cause remains or when it is idiopathic. Serious complications are unusual unless part of the underlying disease. Chronic or recurrent disease is rare. Lesions heal without atrophy or scarring.\textsuperscript{8}

Further reading & references

- Erythema Nodosum; Primary Care Dermatology Society

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