BRITISH JOURNAL OF HOSPITAL MEDICINE

CORE TRAINING FOR DOCTORS

Edited by Dr Daniel JB Marks, Academic Clinical Fellow in Translational Medicine, and **Dr Philip J Smith,** Academic Clinical Fellow and Specialist Registrar in Gastroenterology, University College London

Erythema nodosum

Introduction

Erythema nodosum is the commonest form of panniculitis (inflammation of fat), and it can be associated with a number of serious and potentially life-threatening systemic diseases. This article will focus on erythema nodosum, but it is important to recognize that this condition represents just one subtype of panniculitis. The many other subtypes are listed in *Table 1* and these are categorized by histological appearances, clinical features and associated medical conditions. The distinguishing histological feature is the specific location of inflammation within the subcutaneous fat. This can either be lobular (inflammatory cells within the subcutaneous fat lobules), septal (inflammation between the lobules) or, as is often the case, mixed lobular and septal.

Erythema nodosum can affect males and females of all ages although it is most common in young females (aged 30–40 years). The overall incidence is 1–5/100 000 per year (Macpherson, 1970; Cribier et al, 1998; García-Porrúa et al, 2000).

Table 1. Most common causes of panniculitis

Septal	Erythema nodosum
	Morphoea or scleroderma
	Polyarteritis nodosa
	Necrobiosis lipoidica
	Eosinophilic panniculitis
	Leukocytoclastic vasculitis
	Rheumatoid nodule
Lobular	Connective tissue disease (e.g. lupus)
	Erythema induratum (tuberculosis)
	Erythema nodosum leprosum (leprosy)
	Pancreatic panniculitis
	Traumatic panniculitis
	Nodular vasculitis
	Infection
	Lipodermatosclerosis
	Malignancy
	Calciphylaxis

Dr Andrew Pink *is Academic Clinical Fellow in Dermatology/MRC Clinical Research Training Fellow and* **Professor Jonathan Barker** *is Professor of Clinical Dermatology at St. John's Institute of Dermatology/King's College London, Guy's and St. Thomas' NHS Foundation Trust, London SE1 9RT*

Correspondence to: Dr A Pink (andrew.pink@kcl.ac.uk)

Clinical anatomy and pathophysiology

Despite being idiopathic in over a third of cases, erythema nodosum can be associated with a number of important underlying medical conditions (listed in *Table 2*). The commonest underlying causes include infections (most commonly streptococcal, particularly in children), sarcoidosis, medications (most commonly the oral contra-

Table 2. Most common causes of erythema nodosum

Idiopathic	
Infections	Group A β-haemolytic Streptococcus
	Yersinia, Campylobacter, Salmonella
	Mycoplasma
	Tuberculosis
	Leprosy
	Viral upper respiratory tract infection
	Coccidioidomycosis
Medications	Oral contraceptive pill
	Antibiotics (penicillin, sulphonamides)
	Hepatitis B vaccine
Granulomatous disease	Sarcoidosis
Inflammatory bowel disease	Ulcerative colitis
	Crohn's disease
Autoimmune or rheumatological disease	Lupus
	Sjögren's syndrome
	Behçet's disease
Malignancy	Acute myeloid leukaemia
	Hodgkin's disease
Pregnancy	

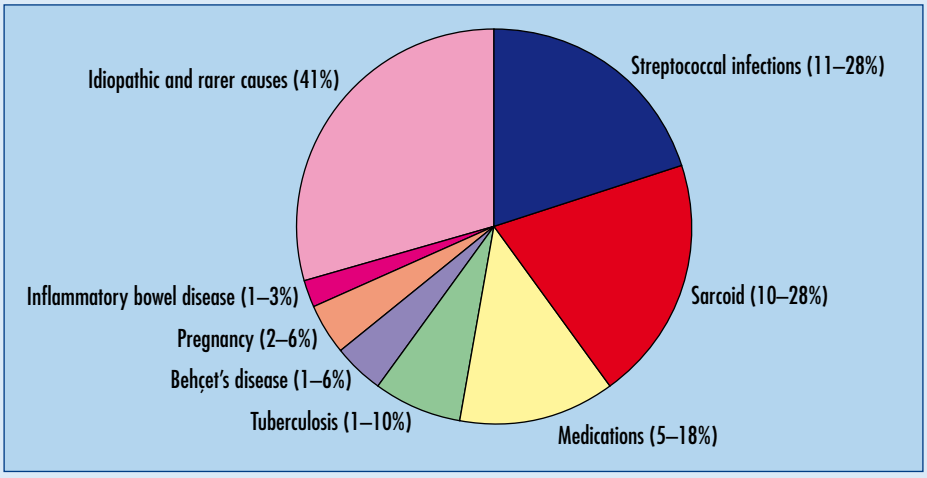

Figure 1. Pie chart showing the causes of erythema nodosum. Data collated from Atanes et al (1991), Cribier et al (1998), Pschos et al (2000), Mert et al (2007).

ceptive pill), autoimmune disorders and inflammatory bowel disease (*Figure 1*). The prevalence of each of these underlying causes varies depending upon the patient population in question. In some cases, such as in those with sarcoidosis, the development of erythema nodosum is associated with an improved prognosis.

The exact pathogenesis remains unclear. It has been proposed that it represents a hypersensitivity reaction to a variety of antigens (Honma et al, 1993; Braverman, 1999; Requena and Sanchez, 2001), such as β-haemolytic streptococcus in the context of infection. Immune complex deposition in septal vessel walls may result in panniculitis (Hedfors and Norberg, 1974). The activated neutrophils present in early lesions may contribute to tissue damage through their production of reactive oxygen intermediates (Kunz et al, 1999).

The main histopathological feature is a septal panniculitis with no associated vasculitis. The septa within the subcutaneous fat are infiltrated with inflammatory cells, comprising predominantly neutrophils in the acute stage and lymphocytes in the latter stages (Forstrom and Winkelmann, 1977).

Figure 2. Classical appearance of erythema nodosum on the lower legs. Erythematous nodules are present over the anterior shins and calves.

Clinical history

Erythema nodosum presents with bilateral, tender, subcutaneous, erythematous nodules on the shins (*Figure 2*). These can measure up to 5 cm in diameter and occasionally coalesce. The site of the lesions helps differentiate erythema nodosum from other forms of panniculitis but it is important to note that lesions can appear on the forearms and thighs in erythema nodosum. Patients often report associated malaise, fever and arthralgia and these symptoms can develop up to 3 weeks before cutaneous features appear. The history is usually acute and lesions commonly resolve within 3–4 weeks. Chronic and recurrent forms can develop, most commonly in idiopathic cases. Lesions flatten and heal with a bruised-like appearance but do not ulcerate or scar. A characteristic feature of this condition is that lesions of varying ages can usually be seen at any one time. The questions listed in *Table 3* should form part of your history.

Examination

The skin

Examine the relevant area, but also perform a wider examination looking for more affected areas and skin manifestations of other diseases (e.g. photosensitive rashes in lupus, lupus pernio in sarcoidosis and pyoderma gangrenosum associated with inflammatory bowel disease). The skin findings may be very subtle and palpation is often very helpful, revealing heat, tenderness and subtle subcutaneous swellings.

Other areas

Once you are happy with the diagnosis you should be thinking about and hunting for an underlying cause. Broad inspection of the patient may help to direct your further examination. Does he/she have signs of iritis

Table 3. History taking from patients with possible erythema nodosum

Question	Why
When did it start?	Usually acute onset
Where did it start?	Usually starts on the shins, this helps to differentiate it from other forms of panniculitis
Are the lesions tender?	Usually tender
Are there any associated symptoms?	Fever, malaise, headache, gastrointestinal upset, arthralgia
Questions to identify underlying cause	**Condition**
Recent sore throat, upper respiratory tract infection or lower respiratory tract infection	Group A β-haemolytic streptococcus most common
Eye symptoms (iritis) or arthralgia	Sarcoidosis (uveitis)
Bowel symptoms	Inflammatory bowel disease
Other rashes, arthralgia, mouth ulcers	Autoimmune disease, e.g. lupus
Drug history	Oral contraceptive pill, penicillin, sulphonamides

suggesting possible sarcoid? If the patient describes respiratory symptoms, a full respiratory examination may be beneficial, just as an abdominal exam is relevant in those with symptoms of inflammatory bowel disease or gastroenteritis. If you are concerned about an underlying malignancy you should feel for hepatosplenomegaly and lymphadenopathy.

Differential diagnosis

Erythema nodosum follows a very characteristic and recognizable course, but in more atypical cases it can be very difficult to distinguish it from other forms of panniculitis (*Table 1*). These should always be considered if the lesions are sparse, outside of the shins, ulcerating or chronic. Associated medical conditions and the histology can aid diagnosis. Further diagnoses to consider include insect bites and acute urticaria but these conditions are usually associated with extreme pruritus and the skin changes are more superficial.

Investigations

If there is diagnostic uncertainty then a dermatological opinion and a deep elliptical biopsy through one of the more recent lesions can be helpful. Once the diagnosis is established, your further investigations are directed by the history that you have elicited and the potential underlying causes that are most relevant to the patient in front of you. *Table 4* lists some possible investigations that you should consider in patients with erythema nodosum.

In those people with erythema nodosum and hilar lymphadenopathy, sarcoidosis is the most likely cause. Other conditions to consider include lymphoma and infections such as tuberculosis, streptococcus, coccidioidomycosis and histoplasmosis.

Management

Any identified underlying causes should be addressed (e.g. penicillin for streptococcal throat infection) and potential causative drugs should be stopped (remember to ask about the oral contraceptive pill). Further measures are largely symptomatic and include gradient support stockings, elevation of the legs and even bed rest for severe cases. Non-steroidal anti-inflammatory drugs, e.g. ibuprofen, can alleviate symptoms. Oral steroids are rarely required and infection must be excluded before their use. Other treatments, such as oral potassium iodide, tetracyclines, colchicine, hydroxychloroquine, ciclosporin and thalidomide, have been used to some effect (Gilchrist and Patterson, 2010). In most cases the condition resolves over 3–4 weeks, although it can occasionally be recurrent or chronic.

Presenting the findings

Example

A 23-year-old woman presents with a 2-week history of painful, erythematous nodules on both shins associated with malaise, fever and arthralgia. She was previously fit and well and her only regular medication was the oral contraceptive pill which she started 4 weeks ago. On examination there were bilateral, subcutaneous, erythematous nodules measuring up to 5 cm in diameter. She has erythema nodosum, most likely secondary to recently starting the oral contraceptive pill. This treatment should therefore be stopped and alternative forms of contraception considered. BJHM

Table 4. Investigations to be considered

Swabs	Throat swab for streptococcus
Sputum	For acid-fast bacilli
Urine	Early morning urine for acid-fast bacilli
Stool	Stool culture, e.g. for campylobacter, salmonella
Bloods	Full blood count (+/- blood film)
	C-reactive protein
	Erythrocyte sedimentation rate
	Anti-streptolysin O titre (for streptococcal infection)
	Serum angiotensin-converting enzyme level (increased in sarcoidosis)
	Anti-nuclear antigen, extractable nuclear antigen and anti-ds DNA antibodies
	Viral serology
	Pregnancy test
Mantoux test	
Imaging	Chest X-ray

Conflict of interest: none.

Atanes A, Gómez N, Aspe B, de Toro J, Graña J, Sánchez JM, Galdo F (1991) Erythema nodosum: a study of 160 cases. *Med Clin Barc* **96:** 169–72

Braverman IM (1999) Protective effects of erythema nodosum in coccidioidomycosis. *Lancet* **353:** 168

Cribier B, Cailee A, Heid E, Grosshans E (1998) Erythema nodosum and associated diseases. A study of 129 cases. *Int J Dermatol* **37:** 667–72

Forstrom L, Winkelmann RK (1977) Acute panniculitis: a clinical and histological study of 34 cases. *Arch Dermatol* **183:** 909–17

García-Porrúa C, González-Gay MA, Vázquez-Caruncho M et al (2000) Erythema nodosum: etiologic and predictive factors in a defined population. *Arthritis Rheum* **43:** 584–92

Gilchrist H, Patterson JW (2010) Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. *Dermatol Ther* **23:** 320–7

Hedfors E, Norberg R (1974) Evidence for circulating immune complexes in sarcoidosis. *Clin Exp Dermatol* **16:** 493–6

Honma T, Bang D, Lee S, Saito T (1993) Ultrastructure of endothelial cell necrosis in classical erythema nodosum. *Hum Pathol* **24:** 384–90

Kunz M, Beutel S, Brocker EB (1999) Leukocyte activation in erythema nodosum. *Clin Exp Dermatol* **24:** 396–401

Macpherson P (1970) A survey of erythema nodosum in a rural community between 1954 and 1968. *Tubercle* **51:** 324–7

Mert A, Kumbasar H, Ozaras R, Erten S, Tasli L, Tabak F, Ozturk R (2007) Erythema nodosum: an evaluation of 100 cases. *Clin Exp Rheumatol* **25:** 563–70

Pschos DN, Voulgari PV, Skopouli FN, Drosos AA, Moutsopoulos HM (2000) Erythema nodosum: the underlying conditions. *Clin Rheumatol* **19:** 212–16

Requena L, Sanchez YE (2001) Panniculitis. Part I. Mostly septal panniculitis. *J Am Acad Dermatol* **45:** 163–83

KEY POINTS

- Erythema nodosum usually has an acute onset.
- It most commonly affects the anterior shins.
- Always consider the potential underlying causes, commonly infection (streptococcus), sarcoidosis and drugs (oral contraceptive pill).
- Non-steroidal anti-inflammatory drugs can help to alleviate the symptoms.
- The condition usually resolves within 3 weeks.