Review

Erythema Nodosum – A Review of an Uncommon Panniculitis

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Abstract

Panniculitis, inflammation of the subcutaneous fat, is a relatively uncommon condition that usually presents with inflammatory nodules or plaques. Erythema nodosum (EN) is clinically the most frequent form of panniculitis and is considered a reactive process that may be triggered by a wide variety of stimuli. Whilst up to 55% of EN is considered idiopathic, the most common causes include infections, drugs, systemic illnesses such as sarcoidosis and inflammatory bowel disease, pregnancy, and malignancy. EN typically presents in the teens and 20s, and is seen more commonly in females. It is often preceded by a non-specific prodrome of one to three weeks, which may include fever, malaise, and symptoms of an upper respiratory tract infection. Cutaneous lesions then follow, typically localized on the extensor aspect of the limbs. The lesions are painful rounded or oval, slightly raised, non-ulcerative red nodules. The exact pathogenesis of EN is not understood, although is thought to result from deposition of immune complexes in the venules of the septae in subcutaneous fat, causing a neutrophilic panniculitis. The classical histopathological picture is of a septal panniculitis without vasculitis. However, the pathological features vary with the chronology of the lesions. Even without specific therapy for a causative condition, EN typically resolves without treatment. Therefore, symptomatic support is adequate for the majority of patients.

Introduction

Panniculitis, inflammation of the subcutaneous fat, is a relatively uncommon condition that usually presents with inflammatory nodules or plaques. A wide variety of subtypes of panniculitis exist, including panniculitis related to infection, external insults, malignancy, and inflammatory diseases.

Erythema nodosum (EN) is clinically the most frequent form of panniculitis and is considered a reactive process that may be triggered by a wide variety of stimuli. Whilst up to 55% of EN is considered idiopathic [1], the most common causes include infections, drugs, systemic illnesses such as sarcoidosis and IBD, pregnancy, and malignancy (see Table 1 for abbreviations). EN typically presents in the teens and 20s and is seen more commonly in females [1-3]. It is often preceded by a non-specific prodrome of one to three weeks, which may include fever, malaise, and symptoms of an upper respiratory tract infection [1-4]. Cutaneous lesions then follow, typically localized on the extensor aspect of the limbs. The lesions are painful rounded or oval, slightly raised, non-ulcerative red nodules [1, 4]. A crop of nodules may last between two to six weeks. They are self-limiting and regress without ulceration, scarring, or atrophy. However EN may recur.

Table 1. Abbreviation/ Acronyms in this article	
ASOT	Antistreptolysin-O titer
BD	Twice daily
EN	Erythema nodosum

ESR	Erythrocyte sedimentation rate
IBD	Inflammatory bowel disease
NSAIDs	Non-steroidal anti-inflammatory drugs
OD	Once daily
TNF	Tumor necrosis factor

Epidemiology

EN is seen more frequently in females (ratio 5:1) [1, 3] and has a peak incidence between the ages of 18 and 34 years [1, 3, 5, 6]. Familial EN has been reported [7], with affected family members showing a common HLA haplotype. The incidence of EN has decreased in the antibiotic era, with a current annual incidence of 1 to 5 per 100,000 persons [1, 5, 6].

Etiology and Pathogenesis

EN is likely a delayed hypersensitivity reaction, which can be triggered by a variety of antigens (Table 2) [1-3, 8-13]. Between 17% and 72% of cases are idiopathic [1-3]. EN is most commonly associated with streptococcal upper respiratory infections; other infectious triggers include Yersinia and Mycobacterium tuberculosis [8, 9, 11, 12]. Triggers for EN are suspected to vary with location, reflecting the geographical distribution of microbes. In the pediatric demographic, infections predominate (up to 68%) [11]. In adults, streptococcal infection usually accounts for 30% of cases. The remaining cases of EN are associated with other infections 5–10%, sarcoidosis 10-35%, rheumatological and autoimmune diseases 5%, inflammatory bowel diseases 2–3%, medications up to 15% (including oral contraceptives), pregnancy 2%, and rarely malignancy [1-3, 8, 9, 12, 14]. There are many single case reports documenting other possible associations, including reports of EN in the setting of vaccinations [15].

Table 2. The most common causes of EN in adults	
Drugs Oral Contraceptive Pill[3,9,12] Penicillin[9,12] Sulphonamides[9,12] **Idiopathic**[1-3, 8, 9, 12, 14] **Infections** Streptococci[1,3,8,9,12] Tuberculosis[1, 8,9,11,12] Upper respiratory tract infections[1,3,9,12] Yersiniosis[1,3]	**Pregnancy**[1,9,12,14] **Systemic Illnesses** Hodgkin's Lymphoma[3,8,9,12] Inflammatory Bowel disease[1,3,8,9,12] Sarcoidosis[1,3,8,9,12]

The exact pathogenesis of EN is not understood, although it is thought that it may be the result of deposition of immune complexes in the venules of the septae of subcutaneous fat, causing a neutrophilic panniculitis [16]. A study of ten patients showed 'primed' neutrophils four times higher than healthy controls [17]. There was also a correlation of primed neutrophils with disease activity; however, this may be cause or effect. There may also be a genetic predisposition to EN. In a study that examined genetic polymorphisms associated with high TNF-α production in a group of patients with EN, with or without sarcoidosis, there was a strong correlation of sarcoidosis-associated EN with TNF αII allele [18]. Furthermore, reports of concurrent Sweet's syndrome and EN have been published and possible etiological and pathogenic associations between the two reactive dermatoses have been proposed [19].

Clinical Features and Diagnosis

EN was initially described by Willan in 1798 [20] and was further discussed in 1842 by Wilson, who believed EN to be a type of erythema multiforme. In 1860, Hebra went on to describe the clinical manifestations of the condition and suggested 'dermatitis contusiformis' [21].

EN typically manifests with a sudden onset of painful, warm, erythematous, nodules and plaques, typically on the shins, knees, and ankles (Figure 1). Lesions may occur at any body site, including the face [1, 22, 23]. The nodules are often more easily palpated than visualized and are typically bilateral and symmetrical, ranging between one and five centimeters in diameter. The nodules may coalesce to form plaques. In the majority of cases, the lesions become bruise-like and then resolve without scarring over a two- to eight-week period. This bruise-like transformation, sometimes known as 'erythema contusiformis', is characteristic of EN and can be helpful for a retrospective diagnosis [3, 4].

Figure 1. Painful erythematous nodules on the anterior lower legs.

In addition to the cutaneous symptoms of this disease, prodromal symptoms of fatigue and malaise or symptoms of an upper respiratory tract infection may often precede the eruptions by one to three weeks. The clinical picture is that of a nonspecific systemic illness, with low-grade fever (60%), malaise (67%), arthralgias (64%), and arthritis (31%) [24]. Pulmonary hilar adenopathy may develop as part of the hypersensitivity reaction of EN and is most commonly seen with sarcoidosis, but may be seen with other causes too.

Cases with a classic presentation and evolution typically do not require biopsy because the condition can be confidently diagnosed on clinical grounds alone. A medication history is necessary to rule out drug etiology. Other forms of panniculitis are the main diagnostic consideration on the legs and primary infective processes must be considered at any body site. Initial evaluation should include throat bacterial culture, ASO titer, chest radiograph, tuberculin skin test, and ESR. Patients with gastrointestinal symptoms should have a stool culture. When the etiology is in doubt, infectious serology should be performed for those microbiological infections more prevalent in the area.

The cases that are referred for a specialist dermatologic opinion are more likely to have an atypical clinical appearance or natural history. A biopsy to confirm the diagnosis and rule out other diagnostic possibilities will often be helpful in these cases.

Some studies from the 1950s through 1980s describe another clinical variant of EN, namely erythema nodosum migrans [25-27]. The proposed histopathological and clinical features of this variant are likely observations of classic EN in different stages of evolution [28]. A rare form of EN involving a palmoplantar distribution, often unilateral, is seen in children, usually after physical activity. There are similar histopathological features to classic EN [29].

Histopathology

The histopathology of EN is quite varied and may require more than one biopsy to sample diagnostic material. Biopsies are commonly non-diagnostic owing to poor technique in performing the biopsy or reluctance in taking a large enough biopsy. Clinicians are often reluctant to take a large biopsy from inflamed/edematous skin from the lower leg for fear of poor wound healing, dehiscence, or poor cosmetic outcome [30]. The best technique is to perform an incisional biopsy extending to the level above the fascia. This technique will provide a specimen that should adequately sample subcutaneous lobules and septa. A punch biopsy will often provide a sample of lower diagnostic yield because a more superficial sample maybe taken and less tissue is available for assessment.

The classical picture is of a septal panniculitis without vasculitis [31–34]. The histologic features of EN can be explained by the chronology of lesions [35]. Early lesions demonstrate septal edema and a lymphohistiocytic infiltrate, with an admixture of neutrophils and eosinophils. The inflammation is typically concentrated at the periphery of the septae and spreads into surrounding fat lobules between adipocytes (Figure 2). There may be edema and lymphocytic infiltration of the walls of veins, although the degree of vascular involvement is variable [31-34].
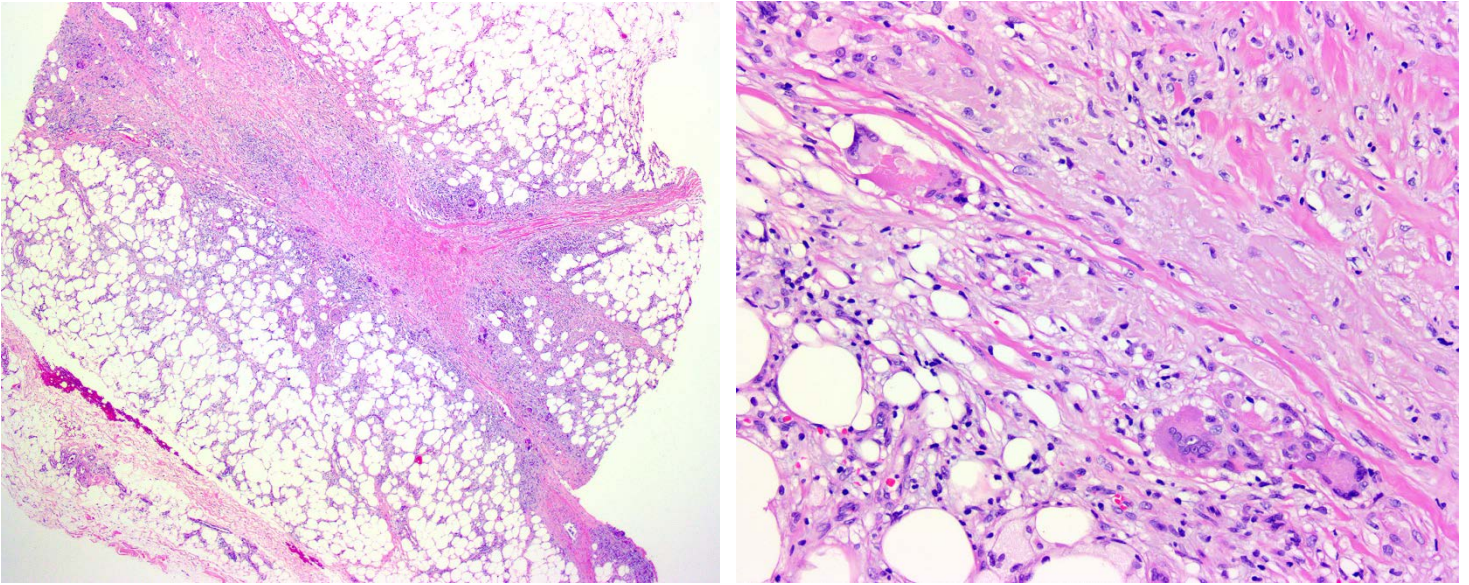

Figure 2. Widened fibrous septa with spill over into the periphery of lobules

Figure 3. This septa shows changes of late stage EN with multinucleated giant cells, lymphcytes and an occasional neutrophils.

Older lesions show fewer vascular changes and a shift from a primarily neutrophilic infiltrate to one of lymphocytes and histiocytes (Figure 3). Histiocytes may display multinucleation or a 'foam-cell' appearance. In some cases, this lymphohistiocytic lobular infiltrate may predominate [34]. Septae are widened, with peripheral fibrosis, and inflammation extends into the periphery of fat lobules. Miescher's radial granulomata can also be seen [31-34, 36, 37]. Although characteristic of EN, they are also seen in other disorders that might clinically resemble EN, such as erythema induratum, nodular lesions in nephrogenic systemic fibrosing dermopathy, Sweet syndrome, and Behçet disease.

Differential Diagnosis

The differential diagnosis includes other forms of panniculitis, especially nodular vasculitis, subcutaneous infections owing to bacteria or fungi, superficial thrombophlebitis, and cutaneous vasculitides [4, 38-42]. Nodular vasculitis is distinguished from EN with involvement of the calves and the presence of ulceration; it more frequently recurs [43]. However, some authors have indicated considerable overlap between the clinical appearances of these entities [13]. Mycobacterium tuberculosis (erythema induratum of Bazex) is also a leading cause of nodular vasculitis. However, it may also be a trigger for EN. A study of 154 patients with tender cutaneous nodules on the legs by Eimpunth et al [42] showed that inflammatory causes predominate (84.4%; panniculitis, vasculitis and granulomas), followed by tumors (6.5%; lymphoma, leukaemia, and leiomyoma), and infections (5.8%; mycobacteria and fungal). EN was the most common diagnosis, representing 30.5% of the patients in this case study. The authors conclude that histopathological investigation is crucial for a definitive diagnosis in patient with tender leg nodules.

Treatment

The evidence for pharmacologic treatment of EN is based almost exclusively on small observational studies. Hence, the choice of agent, dose, and duration is a matter of personal preference.

Even without specific therapy for a causative condition, EN typically resolves without treatment, therefore symptomatic support is adequate for the majority of patients. If there is a treatable, or removable (e.g. medication) cause then this should be addressed; rapid resolution is anticipated. Compression bandages and elevation reduce edema and pain.

NSAIDs such as indomethacin 100mg to 150mg per day or naproxen 250mg BD may be used [44] as an anti-inflammatory and for pain relief. Potassium iodide 360–900 mg/day (although not readily available in Australia) may be of benefit [45, 46]. The mechanism for potassium iodide in improving EN has not been confirmed. However, potassium iodide has been suggested to release heparin from mast cells, suppressing delayed hypersensitivity reactions. Potassium iodide may produce a goiter in utero and is contraindicated during pregnancy. Severe hypothyroidism secondary to exogenous intake of iodide has been also been described [47]. Most commonly potassium iodide may cause abdominal pain, diarrhea, nausea, and vomiting. Other, less common side effects include urticaria and angioedema, swelling of the limbs, face, lips, tongue, throat, and lymph glands [48].

Colchicine 2 mg daily for 3 days, then 1 mg daily for 2 to 4 weeks was used more commonly in the past however now is not used as frequently for neutrophilic dermatoses [49]. Heparin under occlusion has been suggested as a topical agent [33]. Dapsone 100mg daily and hydroxychloroquine 200 mg BID are used in chronic or recurrent cases. A brief course of systemic corticosteroids is infrequently required and may exacerbate an infectious trigger such as tuberculosis. Intralesional corticosteroids may be of benefit for recalcitrant nodules. Recent reports include use of anti-TNF biological agents [50, 51], especially in patients with active IBD. However, these are contraindicated in the presence of infections (in particular tuberculosis should be excluded) [51]. Case reports suggest that thalidomide and methotrexate may be of benefit. Treatment options during pregnancy should be restricted to non-pharmacological means,.However, in cases where this is not sufficient, discussions in conjunction with an obstetrician about the risks and benefits of potential drug regimens are recommended [10]. A summary of treatments is depicted in Table 3.

Table 3. Treatments for Erythema Nodosum	
First Line Agents	NSAIDs (3)
Second Line Agents	Colchicine (2)
	Potassium iodide (2) (may not be available)
Topical Agents	Heparinoid ointment under occlusion (3)
Severe Disease	Prednisone (3)
Recalcitrant Nodules	Intra-lesional corticosteroid (3)
Chronic/ Recurrent Disease	Dapsone (3)
	Hydroxychloroquine (3)
Other agents	Anti- TNF monoclonal antibodies (3)
	Thalidomide (3)
	Methotrexate (3)
Level of evidence: 1. double-blind studies; 2. case series; 3. case reports.	

Conclusion

EN is a relatively uncommon dermatological condition found more frequently in younger females. The typical presentation consists of painful rounded or oval nodular erythematous lesions on the lower limbs and often follows a non-specific prodromal phase. The differential diagnosis includes erythema induratum and cutaneous vasculitis. Streptococcal infections are the most common cause identified, but most cases are idiopathic. The diagnosis is usually made clinically without biopsy. Quality evidence for treatment is lacking, although most cases resolve without intervention. Symptom relief is therefore the mainstay of treatment of most patients.

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