

# CUTANEOUS INFECTIONS IN LYMPHOEDEMA

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The typical diagnosis of skin infection in patients with lymphoedema includes erysipelas and cellulitis, but the true picture is more complex with the possibility of secondary complications such as lymphadenitis (adenolymphangitis) and lymphangitis. The recent description of acute inflammatory episodes (or AIEs) has gone some way to explaining how a patient may be prone to rapid-onset febrile illness (Mortimer, 2000). This review summarises the current understanding of cutaneous infections and inflammatory presentations that are observed in lymphoedema and discusses associated immunological compromises.

## Key words

Lymphoedema  
Cellulitis  
Erysipelas  
Acute inflammatory episodes

In 1999 the worldwide incidence of lymphoedema was estimated at 140 million per annum, with the perception that it was a rare condition in Europe (Boccardo et al, 1999). It has since become clear that these estimates were far too low and that lymphoedema and veno-lymphatic dysfunction are far more common than expected (Moffatt et al, 2003). Problems in accurately mapping the epidemiology of this disease arise from difficulties in formulating a concise definition, the varied nature of published epidemiological studies and the ambiguity of the terminology that has been utilised (Franks et al, 2006).

Lymphoedema is essentially a condition in which tissue is distended by the presence of lymph or interstitial fluid. It is a chronic and progressive disease that usually develops when a

major component of the lymphatic system (especially in the axilla or groin) becomes obstructed and the drainage of lymph is interrupted so that the fluid accumulates in tissue. There are multiple causes of obstruction such as tumour masses (either within lymphatic vessels and tissue or in neighbouring tissue), excess adipose tissue, surgical removal of lymph nodes and associated vessels, the presence of fibrous scar tissue (a result of chronic inflammation or radiation therapy), and infection with parasitic worms. Prolonged lymphatic obstruction leads to continued dilation of lymphatic vessels and may result in increased deposition of fibrotic material because lymph characteristically has a high protein content which is thought to stimulate fibrogenesis. Hence, the patient presents with swollen limbs or trunk containing either excessive fluid and/or fibrotic material.

Lymphoedema develops by several routes. It can be a congenital condition that normally affects a single limb, although more extensive involvement is possible (Connell et al, 2008). This is commonly known as primary lymphoedema and may not be manifest immediately at birth. Either a malformation or hypoplasia of the lymphatic system can give rise to primary lymphoedema. It is a relatively uncommon disease, with prevalence in people under 20 of age reported to be 1.15/100,000 (Smeltzer et al, 1985).

Secondary lymphoedema has diverse origins and develops in individuals who previously had a 'normal' lymphatic system. Lymphatic filariasis (also known as elephantiasis) is an infection of the lymph nodes which is caused by nematode worms (most commonly *Wuchereria bancrofti*). It is transmitted to man when filarial larvae are introduced, mainly into lower limbs, by the bite of an infected mosquito and the infection becomes apparent about a year later. Some patients demonstrate more extensive sequelae than others, ranging from few clinical signs to extensive inflammatory responses. Fever, rashes, eosinophilia, lymphangitis and lymphadenitis can occur and repeated episodes can lead to extensive fibrosis and blockage of lymphatic ducts, which results in gross enlargement of limbs (Partano, 1987; Pani and Srividya, 1995). Usually the lower limbs are most seriously affected. This type of lymphoedema is endemic in some tropical and subtropical areas.

Many forms of lymphoedema are secondary to malignancies, particularly following surgical removal of lymphatic tissue and after radiotherapy. Between 25 and 33% patients who undergo surgery for breast cancer are expected to develop lymphoedema in the arm or trunk and the risk factors have been identified (Franks et al, 2003).

Another causative factor in the development of lymphoedema is

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morbid obesity (Ryan, 2002). In enlarged limbs with redundant skin folds and excess adipose tissue, components of the lymphatic system can become obstructed and this can initiate lymphoedema or exacerbate existing secondary lymphoedema (Fife et al, 2008). Furthermore, the inability of the morbidly obese to cope with compression garments and their increasing immobility contributes to increasing limb size and weight, with knock-on effects on lymphoedema and venous insufficiency (Fife et al, 2008). Whether obesity and lymphoedema are genetically linked is not known.

### Infections associated with lymphoedema

The skin is a natural barrier to infection that is known as the first line of defence. Infections associated with the cutaneous layers are caused either by ingress of infectious agents through breaches in this mechanical barrier; or else delivered systemically in blood vessels. The human immune response depends on the two integrated protective mechanisms to the presence of agents capable of causing infection: innate and acquired immunity. When these defence mechanisms are overcome or evaded, infection results. On the basis of their location and presentation, infections and inflammation in lymphoedema patients can be distinguished as erysipelas, cellulitis (Figure 1), lymphangitis and lymphadenitis. The term 'acute inflammatory episode' or AIE has been coined to describe a secondary acute inflammation which can be distinguished from chronic inflammation. The AIE has been considered separately from overt infection; however, a recent consensus document suggested that it was synonymous with cellulitis (British Lymphology Society [BLS], 2008).

Erysipelas is a well known infection of the superficial layers of the dermis that is caused by *Streptococcus pyogenes* (a member of the beta haemolytic group A streptococci). It usually develops rapidly within 24 to 48 hours of bacterial invasion and it is mainly characterised by a peripherally spreading, hot, bright red, oedematous, infiltrated and sharply circumscribed plaque that has a raised border. Blistering of the affected area may

occur (Figure 2). Lymphatic involvement is usual, with lymphangitis and lymphadenitis possible. Often the patient is febrile and may also exhibit malaise and chills. In the past, erysipelas was known as St Anthony's fire. Treatment with penicillin (intravenous for a severe infection, otherwise intramuscular or oral penicillin) usually results in rapid resolution of symptoms. Swelling may persist after the infection has resolved.

Cellulitis is an acute, diffuse, spreading, oedematous, suppurative infection of deeper subcutaneous tissues and fat. It may sometimes involve muscle and be associated with abscess formation. Cellulitis develops more slowly than erysipelas, blistering rarely occurs and the border of the affected area is not well defined. Again, the patient may appear unwell and describe an acute febrile episode before the development of the lesion on the skin. Causative agents largely responsible are *Streptococcus pyogenes* and *Staphylococcus aureus*, but other bacteria, such as Gram negative bacilli, can be implicated. Cellulitis often follows loss of skin integrity, with streptococcal infection associated with small breaks and staphylococcal infection with more extensive skin damage (Grey, 1998). Treatment with penicillin is indicated, unless *S. aureus* is confirmed, but a slower recovery will be seen compared to erysipelas. Hospital admission for treatment is not unusual. Lymphoedema patients are susceptible to repeated skin infections, yet the impact of these events is often underestimated.



Figure 1. Lymphoedema and acute cellulitis. Reproduced by kind permission of Christine Moffatt.

The lymphatic system provides a means of draining fluids, cells and foreign material from interstitial spaces. Hence inflammatory cells and infectious agents will be transported to regional lymph nodes from foci of infection associated with the skin. When infection involves the lymphatic system, two outcomes are possible. Lymphangitis is the inflammation of lymphatic vessels where the channels become dilated and distended by fluid, cellular debris and infective agents moving away from an infected area. Lymphadenitis is the inflammation of lymph nodes which become enlarged and painful with increasing numbers of infective agents. The progressive extension of painful red lines away from an infected



Figure 2. Blistering as a result of erysipelas. Reproduced by kind permission of Val Robson.

lesion towards enlarged and painful lymph nodes characterises acute infection. Most virulent pathogens can cause this effect, but the beta haemolytic streptococci are commonly involved. Diagnosis always warrants immediate and vigorous antibiotic intervention.

### Acute inflammatory episodes

Recurrent febrile episodes were noted in lymphoedema patients in 1963 (Edwards, 1963).

More recently, AIEs have been recognised as attacks of apparent infection that affect lymphoedema patients (Mortimer, 2000). AIEs have also been called cellulitis, lymphangitis, episodic dermatolymphoangioadenitis, erysipelas and pseudo-erysipelas. They are characterised by extremely rapid onset, so that within 30 minutes of the onset of flu-like symptoms the patient may be markedly unwell and be exhibiting a fever, vomiting and delirium, together with a painful, swollen, erythematous skin infection. These events develop so quickly in lymphoedema patients that many carry antibiotics with them at all times so that they can self-medicate immediately. Unfortunately, AIEs are not consistent in their characteristics. Sometimes pain without overt inflammation can occur and in other cases a low grade 'grumbling' condition continues for more lengthy periods until it is resolved by antibiotics. Typically, AIEs are recurrent and length between episodes varies from a few weeks to more than a year (Mortimer, 2000). In lymphoedema, AIEs can be distinguished from classical erysipelas or cellulitis by the absence of a spreading, erythematous margin.

### Predisposing factors for erysipelas, cellulitis and AIEs

Risk factors for episodes of recurring infection in lymphoedema patients are numerous. Minor skin injuries, nematode infection and skin diseases, such as fungal infections have been implicated. Venous insufficiency, obesity, diabetes, immunosuppression, respiratory infections and alcoholism have also been identified as important risk factors.

The first case-controlled study of risk factors for erysipelas of the leg emphasised lymphoedema and site of

entry (Dupuy et al, 1999). It was a multi-centred study in which 167 patients that were hospitalised for erysipelas of the leg were compared to 294 controls. Using multivariate analysis associations between local risk factors (history of leg surgery, radiotherapy, neurological disorders, leg thrombophlebitis, leg ulcers, pressure ulcers, leg oedema, lymphoedema, leg dermatosis, toe-web intertrigo, varicose veins or varicosities) and general risk factors (diabetes mellitus, obesity, smoking, sedentary occupation or alcohol misuse) were investigated. Seated position at work, diabetes mellitus, alcohol misuse and smoking were not found to be associated with erysipelas of the leg. Lymphoedema was shown to be the most prominent risk factor (present in 18% of patients), and the presence of an entry site (mainly fungal infections of toe webs) another important factor (Dupuy et al, 1999).

A prospective case-controlled study of risk factors for acute cellulitis identified strong risk factors to be previous history of cellulitis, leg ulcer or saphenectomy, and the presence of possible sites of entry (dry skin, leg lesions or intertrigo) (Björnsdóttir et al, 2005). One hundred hospitalised cellulitis cases were compared to 200 control patients. Culture of toe web specimens showed that the presence of dermatophyte infections was found to be more common in cellulitis patients, and that *S. aureus*,  $\beta$ -haemolytic streptococci and Gram negative bacilli were isolated from toe webs. This suggests a likely entry point for the causative agents of cellulitis, since dermatophyte infections tend to cause cracks and fissures that disrupt the integrity of skin between toes (Björnsdóttir et al, 2005).

A recent study investigated the link between erysipelas and lymphatic impairment by examining patients with erysipelas of unknown origin for pre-existing lymphatic insufficiency in their unaffected limb (Damstra et al, 2008). None of the 40 subjects included in this prospective study had clinical signs of lymphoedema or any of the predisposing comorbidities listed above as risk factors for erysipelas or cellulitis. Both legs of each patient were examined by lymphoscintigraphy four

months after the onset of an episode of erysipelas in one leg and, of 33 patients with impaired lymphatic function in the previously infected leg, 26 had impaired lymphatic function in their uninfected leg. Therefore, it seems appropriate that patients presenting with a first episode of erysipelas investigation for pre-existing lymphatic dysfunction of both legs be prioritised because the infection may signal the presence of underlying lymphoedema (Damstra et al, 2008). These authors recommended that, 'treatment of erysipelas should focus not only on the infection, but also on the lymphological aspects, and long-standing treatment for lymphoedema is essential in order to prevent recurrence of erysipelas and aggravation of the pre-existing lymphatic impairment'.

A similar study in which patients hospitalised with lower limb cellulitis were investigated for lymphatic abnormalities by lymphoscintigraphy found a strong association between abnormalities in lymph drainage and lower limb cellulitis (Soo et al, 2008). Although this was a small study with only 30 patients, none had a prior diagnosis of lymphoedema, yet 13/15 had abnormal scans and seven had clinical lymphoedema.

Whether infected patients had previously unrecognised lymphatic abnormalities that increased their susceptibility to erysipelas and cellulitis may be difficult to determine, because the infections may cause lymphatic damage that precipitates secondary lymphoedema (Keeley, 2008). Either way, early diagnosis provides the opportunity to prevent recurring infections that aggravate lymphatic damage. The use of compression garments after an episode of erysipelas has been advocated (Damstra et al, 2008), and larger studies are indicated (Soo et al, 2008).

### Management of erysipelas, cellulitis and AIEs

The diagnosis and treatment of cellulitis have been outlined in guidelines such as those of CREST (Clinical Resource Efficiency Support Team) in 2005 (available online at: [www.gain-ni.org/Guidelines/Management\\_Cellulitis\\_Adults.asp](http://www.gain-ni.org/Guidelines/Management_Cellulitis_Adults.asp)). Recently, the British Lymphology society (BLS) has also issued guidelines



for assessment and management of cellulitis (available online at: [www.thebbs.com/concensus.php?bbs\\_user=d7be61a7e9bef06638316907afd02364](http://www.thebbs.com/concensus.php?bbs_user=d7be61a7e9bef06638316907afd02364)).

The speed and severity of skin infections in lymphoedema patients demand rapid antibiotic intervention, often on an empirical basis. The long-term use of prophylactic strategies to reduce the number and severity of infections in lymphoedema patients was recommended for patients suffering more than two episodes of cellulitis within 12 months (BLS, 2007). A review of the clinical evidence for the efficacy of antibiotics and anti-inflammatory agents demonstrated inadequacies (Badger et al, 2009). Only four randomised controlled studies were included: two studied the effects of physical treatment and selenium or a placebo in preventing AIEs and two concerned ivermectin and diethylcarbamazine (anti-parasite drugs) and penicillin to prevent lymphadenitis. No treatments were shown to give statistically significant reductions in AIEs in the limbs of lymphoedema patients and the need of further clinical evidence was identified (Badger et al, 2009). The skin hygiene of patients with enlarged limbs is an area of concern in preventing infection. Foot care was found to be important in preventing recurrent infections, especially if combined with penicillin and this finding was suggested to have relevance to the care of arms in breast cancer patients (Badger et al, 2009).

### The role of the lymphatic system in defence mechanisms

The lymphatic system is actively involved in many physiological and pathological processes, including cancer metastasis and inflammation (Alitalo et al, 2005). It plays an important role in removing fluid that contains complex macromolecules from the spaces between cells in tissues (tissue homeostasis) and in delivering vital components of the immune response to allergenic substances; in particular, the mediation of the afferent immune response via recruitment of antigen-presenting cells (typically Langerhans cells) towards the lymph nodes (Halin and Detmar, 2006; Jurisic and Detmar, 2009). Interruption of normal function or dysfunction caused

by obstruction is likely to have a knock-on effect to immune competency. For example, an investigation into cutaneous cell-mediated immunity in 35 women with post-mastectomy lymphoedema confirmed this assumption (Mallon et al, 1997). Thirty-five patients were randomly divided into two groups to test their afferent sensitisation, and the function of the efferent loop of the allergic contact dermatitis response using exposure to dinitrochlorobenzene (DNCB). Abnormal responses to the sensitising agent demonstrated that suppressed immune competence was found in the lymphoedematous limb compared to the unaffected limb (Mallon et al, 1997). The likely mechanism is the impaired migration of dendritic (Langerhans) cells to the draining lymph nodes via lymphatic vessels, and the resultant sub-optimal encounter with naive T-cells (Randolph et al, 2005; Swartz et al, 2008). However, the underlying mechanisms for the loss of immunocompetency are not fully understood and further research is needed.

Both chronic and acute skin inflammation have been linked closely with lymphatic function (Jurisic and Detmar, 2009). The role of lymphangiogenesis in inflammation seen in lymphoedema is not clear. Chemokines such as nuclear factor kappa B (NF- $\kappa$ B) and tumour necrosis factor alpha (TNF- $\alpha$ ) may be important contributors (Ji, 2007). This may be an important factor in the development of AIEs where vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor has been found to be an effective treatment (Halin et al, 2008). Using an animal model of lymphoedema, Tabibiazar et al (2006) have demonstrated that impaired mobility of immunocompetent cells leads to intense inflammatory changes. However, these results need to be translated into the situation in humans.

### Conclusion

This review illustrates the difficulties associated with the management of cutaneous infections in lymphoedema, and, in our understanding of AIEs. Our knowledge of the complex risk factors is increasing, and the contribution of the repeated infections and acute

### Key points

- ▶ Infections such as cellulitis and erysipelas can develop very quickly in lymphoedema.
- ▶ The acute inflammatory episode is a frequent characteristic in lymphoedema: clinicians and patients should be informed and alert to it and prepared to treat immediately.
- ▶ In the presence of lymphoedema, antigen presentation, particularly of pathogens, is abnormal.

inflammation to lymphatic deterioration are beginning to be understood. The need to prevent and manage these events effectively is evident but not universally realised. JL

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PROMOTING PROFESSIONAL LYMPHOEDEMA SERVICES

## BLS Lymphoedema Awareness Week

20 April 2009 signals the start of the British Lymphology Society's Lymphoedema Awareness Week

– the week in the year which will draw attention to the 120,000 men women and children in the UK and Ireland who suffer from Lymphoedema.

Lymphoedema causes swelling of the limbs and body and remains an underestimated and largely misunderstood health problem – many health care practitioners have problems with its diagnosis and treatment.

BLS are publishing the "5 Guides"; one for GPs and one for patients, which have been drawn up in consultation with partners in the Lymphoedema Support Network and Macmillan. The Guides will each flag the five key things the target audience need to know about Lymphoedema and will be backed by a dedicated website – [www.blsawarenessweek.co.uk](http://www.blsawarenessweek.co.uk)

The Guides will be launched at the prestigious International Lymphoedema Conference being hosted by WoundsUK at Ascot Racecourse on 21/22/23 April.

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