Narrative Review: Diseases That Masquerade as Infectious Cellulitis
Matthew E. Falagas, MD, MSc, and Paschalis I. Vergidis, MD

For cellulitis that does not respond to conventional antimicrobial treatment, clinicians should consider, among other explanations, several noninfectious disorders that might masquerade as infectious cellulitis. Diseases that commonly masquerade as this condition include thrombophlebitis, contact dermatitis, insect stings, drug reactions, eosinophilic cellulitis (the Wells syndrome), gouty arthritis, carcinoma erysipelatoides, familial Mediterranean fever, and foreign-body reactions. Diseases that uncommonly masquerade as infectious cellulitis include urticaria, lymphedema, lupus erythematosus, sarcoidosis, lymphoma, leukemia, Paget disease, and panniculitis. Clinicians should do an initial diagnostic work-up directed by the findings from a detailed history and complete physical examination. In many cases, skin biopsy is the only tool that helps identify the correct diagnosis. Special tests may also be needed.

For author affiliations, see end of text.

Cellulitis, an inflammatory disease that involves the skin and subcutaneous tissues, frequently leads to office visits and hospital admissions. The term *erysipelas*, a distinct type of inflammatory disease more superficial than cellulitis, is reserved for cutaneous infection mainly due to *Streptococcus pyogenes*. Most cases of cellulitis can be attributed to an infectious cause. However, physicians may be challenged by cases that do not respond to the initial antimicrobial regimen. In addition to considering inappropriate empirical antimicrobial treatment, poor patient adherence, antibiotic resistance, underlying deep-seated infection, foreign body–related infection, and depressed immune status, physicians should also consider a broad spectrum of noninfectious causes that masquerade as infectious cellulitis. They should take into account several vascular, primary dermatologic, rheumatic, immunologic–idio–pathic, malignant, familial, and other diseases that commonly (Table 1) or uncommonly (Table 2) masquerade as infectious cellulitis. The literature lacks data about the relative frequency of infectious cellulitis compared with noninfectious masqueraders. We review the diseases that mimic infectious cellulitis and may present a diagnostic challenge to physicians.

**Methods**
We identified data by searching PubMed (from 1950 until April 2004), Current Contents, and references from relevant articles. The main search terms were *cellulitis*, *erysipelas*, *non-infectious*, *thrombophlebitis*, *contact dermatitis*, *Wells syndrome*, *Sweet syndrome*, *familial Mediterranean fever*, *foreign-body reaction*, *lymphoma*, *leukemia*, *panniculitis*, and *Paget disease*. We reviewed English-language papers.

**Diseases That Commonly Masquerade as Infectious Cellulitis**

**Superficial Thrombophlebitis**
Superficial thrombophlebitis, which is often caused by the presence of an intravenous needle or catheter, frequently presents as a red, indurated area (1). A tender cord palpable along the course of the affected superficial vein can help differentiate this disorder from infectious cellulitis. Extension of the inflammation beyond the vein might suggest an infectious process. Superficial thrombophlebitis is treated with anti-inflammatory medications, compression therapy (2, 3), and removal of the intravenous catheter. This condition may be complicated by an infection in which the signs of inflammation persist despite treatment of symptoms. In such cases, antibiotic use is appropriate.

Superficial migrating thrombophlebitis presents as successive episodes of thrombophlebitis involving different veins in different body areas (Trousseau phenomenon). This clinical syndrome may resemble recurrent infectious cellulitis and should prompt a search for underlying diseases, such as thromboangitis obliterans, malignant tumors (4), and hypercoagulable states.

**Deep Venous Thrombosis**
Deep venous thrombosis presents as unilateral leg edema, warmth, or erythema, all of which may be confused with infection (5–7). Tenderness along the involved veins and engorgement of superficial veins are other presenting features that might help in the differential diagnosis of infectious cellulitis. Rarely, a palpable clot may suggest the correct diagnosis. In addition, patients with deep venous thrombosis can have fever due to a systemic inflammatory response; however, body temperature rarely exceeds 38.3 °C. Although leukocytosis suggests infectious cellulitis, this laboratory finding may also occur in patients with deep venous thrombosis. The presence of risk factors such as a hypercoagulable state suggests deep venous thrombosis. However, history and physical examination are of limited value, and an imaging study is frequently needed. Duplex ultrasonography is the initial diagnostic study of choice (8, 9), and heparin is the favored treatment. To prevent recurrences, a 3- to 12-month course of oral anticoagulant therapy should follow heparin treatment (10).

See also:

**Web-Only**
Conversion of tables into slides
Contact Dermatitis

Contact dermatitis, especially in the acute form, may masquerade as cellulitis (11, 12). In toxic or irritant (non-allergic) contact dermatitis, the lesion is sharply demarcated and constricted to the area of exposure. Allergic contact dermatitis is a delayed hypersensitivity reaction and may spread beyond the site of initial contact. Commonly implicated agents include detergents, solvents, disinfectants, metals, and dyes, as well as poison ivy and poison oak.

History of exposure to an irritating agent and the associated pruritus help differentiate contact dermatitis from infectious cellulitis. Skin biopsy and patch testing may confirm the diagnosis (13). Nonetheless, patch testing should be deferred until active lesions have subsided.

Avoidance of exposure is the cornerstone of treatment. Once contact dermatitis has developed, topical corticosteroid preparations are usually effective. Systemic corticosteroids are indicated for severe cases (14, 15). Clinicians should remember that secondary infection may complicate skin barrier disruption elicited by dermatitis (16). In such cases, reemergence of signs of inflammation is evident and antibiotic therapy should be instituted.

Insect Stings or Bites and Other Envenomations

Allergic reactions to insect stings range from mild local erythema to anaphylaxis (17). An extensive local reaction presents as swelling that extends over a large area, peaks within 48 hours, and lasts up to 7 days (18). Such a lesion may resemble infectious cellulitis, which, in fact, infrequently develops after an insect sting. The presence of ascending lymphangitis and lymphadenopathy suggests infection. A common mistake after an insect sting is to treat an infection rather than an allergic reaction. The usual medical treatment for insect stings is antihistamines and acetylsalicylic acid, if necessary. Systemic steroids should be administered for an extensive lesion.

In insect bites, a disturbing local inflammation usually develops but resolves within a few hours. Systemic reactions are extremely rare. The presence of pruritus distinguishes this lesion from infectious cellulitis. Systemic antihistamines are the treatment of choice (19). Other contact reactions, such as caterpillar dermatitis and beetle vesications, can manifest as a cellulitis-like reaction. Envenoma-

Table 1. Diseases That Commonly Masquerade as Infectious Cellulitis

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial thrombophlebitis</td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombophlebitis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary dermatologic disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact dermatitis</td>
<td></td>
</tr>
<tr>
<td>Insect stings or bites and other envenomations</td>
<td></td>
</tr>
<tr>
<td>Drug reactions</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic cellulitis (Wells syndrome)</td>
<td></td>
</tr>
<tr>
<td>Sweet syndrome</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rheumatic disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gouty arthritis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunologic–idiopathic disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromelalgia</td>
<td></td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma erysipelasoides</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Familial syndromes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Mediterranean fever</td>
<td></td>
</tr>
<tr>
<td>Familial Hibernian fever</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Foreign-body reaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction to metallic implant</td>
<td></td>
</tr>
<tr>
<td>Mesh intolerance</td>
<td></td>
</tr>
<tr>
<td>Foreign-body granulomatous reactions (silicone injections, paraffin oils)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Diseases That Uncommonly Masquerade as Infectious Cellulitis

<table>
<thead>
<tr>
<th>Primary dermatologic disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria and angioedema</td>
<td></td>
</tr>
<tr>
<td>Follicular occlusion triad</td>
<td></td>
</tr>
<tr>
<td>Hidradenitis suppurativa</td>
<td></td>
</tr>
<tr>
<td>Acne conglobata</td>
<td></td>
</tr>
<tr>
<td>Dissecting cellulitis of the scalp</td>
<td></td>
</tr>
<tr>
<td>(perifolliculitis capitis abscedens et suffodiens)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphedema</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunologic disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Panniculitis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal</td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td></td>
</tr>
<tr>
<td>Lipodermatosclerosis</td>
<td></td>
</tr>
<tr>
<td>Morphea</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic fasciitis</td>
<td></td>
</tr>
<tr>
<td>Eosinophilia myalgia syndrome</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lobular</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical panniculitis</td>
<td></td>
</tr>
<tr>
<td>Cold-induced</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td></td>
</tr>
<tr>
<td>Chemical</td>
<td></td>
</tr>
<tr>
<td>Factitious</td>
<td></td>
</tr>
<tr>
<td>Postirradiation</td>
<td></td>
</tr>
<tr>
<td>Panniculitis associated with systemic disease</td>
<td></td>
</tr>
<tr>
<td>Pancreatic panniculitis</td>
<td></td>
</tr>
<tr>
<td>Lupus panniculitis</td>
<td></td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td></td>
</tr>
<tr>
<td>Weber–Christian disease</td>
<td></td>
</tr>
<tr>
<td>Cytophagic histiocytic panniculitis</td>
<td></td>
</tr>
<tr>
<td>Post-steroid panniculitis</td>
<td></td>
</tr>
<tr>
<td>Nodular vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
</tr>
<tr>
<td>Paget disease of the breast</td>
<td></td>
</tr>
<tr>
<td>Extramammary Paget disease</td>
<td></td>
</tr>
<tr>
<td>Glucagonoma</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calciphylaxis</td>
<td></td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Diseases That Masquerade as Infectious Cellulitis

Vascular disorders
- Superficial thrombophlebitis
- Deep venous thrombophlebitis

Primary dermatologic disorders
- Contact dermatitis
  - Insect stings or bites and other envenomations
  - Drug reactions
  - Eosinophilic cellulitis (Wells syndrome)
  - Sweet syndrome

Rheumatic disorders
- Gouty arthritis

Immunologic–idiopathic disorders
- Erythromelalgia
- Relapsing polychondritis

Malignant disorders
- Carcinoma erysipelasoides

Familial syndromes
- Familial Mediterranean fever
- Familial Hibernian fever

Foreign-body reaction
- Reaction to metallic implant
- Mesh intolerance
- Foreign-body granulomatous reactions (silicone injections, paraffin oils)

Contact Dermatitis

Contact dermatitis, especially in the acute form, may masquerade as cellulitis (11, 12). In toxic or irritant (non-allergic) contact dermatitis, the lesion is sharply demarcated and constricted to the area of exposure. Allergic contact dermatitis is a delayed hypersensitivity reaction and may spread beyond the site of initial contact. Commonly implicated agents include detergents, solvents, disinfectants, metals, and dyes, as well as poison ivy and poison oak.

History of exposure to an irritating agent and the associated pruritus help differentiate contact dermatitis from infectious cellulitis. Skin biopsy and patch testing may confirm the diagnosis (13). Nonetheless, patch testing should be deferred until active lesions have subsided. Avoidance of exposure is the cornerstone of treatment. Once contact dermatitis has developed, topical corticosteroid preparations are usually effective. Systemic corticosteroids are indicated for severe cases (14, 15). Clinicians should remember that secondary infection may complicate skin barrier disruption elicited by dermatitis (16). In such cases, reemergence of signs of inflammation is evident and antibiotic therapy should be instituted.

Insect Stings or Bites and Other Envenomations

Allergic reactions to insect stings range from mild local erythema to anaphylaxis (17). An extensive local reaction presents as swelling that extends over a large area, peaks within 48 hours, and lasts up to 7 days (18). Such a lesion may resemble infectious cellulitis, which, in fact, infrequently develops after an insect sting. The presence of ascending lymphangitis and lymphadenopathy suggests infection. A common mistake after an insect sting is to treat an infection rather than an allergic reaction. The usual medical treatment for insect stings is antihistamines and acetylsalicylic acid, if necessary. Systemic steroids should be administered for an extensive lesion.

In insect bites, a disturbing local inflammation usually develops but resolves within a few hours. Systemic reactions are extremely rare. The presence of pruritus distinguishes this lesion from infectious cellulitis. Systemic antihistamines are the treatment of choice (19). Other contact reactions, such as caterpillar dermatitis and beetle vesications, can manifest as a cellulitis-like reaction. Enveno-
Diseases That Masquerade as Infectious Cellulitis

Drug Reactions

Rashes are common adverse drug reactions. A fixed drug eruption presents as a well-demarcated plaque that recurs at the same site each time the offending drug is administered (20, 21). The associated itching or burning sensation also helps differentiate this entity from infectious cellulitis. The most commonly affected areas are the lips and the genitalia. Characteristically, the lesions do not spread as rapidly as infectious cellulitis. Healing is usually associated with residual hyperpigmentation. This residual hyperpigmentation indicates site recognition. Medications that are usually implicated include antibiotics (trimethoprim–sulfamethoxazole is the leading agent) and anti-inflammatory drugs. An oral challenge test or topical provocation with drug preparations are reliable diagnostic tools (22, 23). Withholding the offending agent and using topical corticosteroids are the treatment of choice.

Eosinophilic Cellulitis

Eosinophilic cellulitis (the Wells syndrome) is characterized by acute pruritic dermatitis (24, 25). Patients typically present with one or a few erythematous plaques, which may resemble infectious cellulitis. The lesions evolve over 2 to 3 days and resolve completely without scarring in 2 to 8 weeks. The disease usually recurs. Peripheral eosinophilia, manifested during the acute phase, and dermal eosinophilic infiltration help differentiate this entity from infectious cellulitis. The Wells syndrome may be idiopathic or associated with conditions such as myeloproliferative, immunologic, and infectious disorders and with medications (26–28). Most cases respond favorably to oral corticosteroid treatment (29).

The Sweet Syndrome

The Sweet syndrome (acute febrile neutrophilic dermatosis) is characterized by papules that coalesce to form inflammatory plaques (30–32). These lesions are erythematous and tender; they most commonly occur on the upper extremities, face, and neck. Associated findings include fever, conjunctivitis or iridocyclitis, oral aphthae, and arthralgia or arthritis. Patients also have moderate neutrophilia and dermal infiltration by polymorphonuclear leukocytes. Sometimes the syndrome is mistaken for infectious cellulitis (33–35). Ten percent of patients with the syndrome also have an associated malignant condition, usually acute myelogenous leukemia. Immunologic disorders, such as rheumatoid arthritis and inflammatory bowel disease, have also been implicated. Corticosteroids remain the mainstay of treatment (36).

Gouty Arthritis

In acute gouty arthritis, the affected joint is inflamed with prominent overlying erythema and warmth (37). The cutaneous erythema may extend in areas beyond the joint and resemble cellulitis. In addition, gout may affect peri-articular structures and lead to tendonitis and bursitis. Chills, a low-grade fever, and an elevated leukocyte count may occur, mimicking an infection. In differentiating this entity from a skin infection, clinicians should not underestimate the inflammation of the joint. Gouty arthritis is typically monoarticular and predominantly affects the lower extremity, usually the first metatarsophalangeal joint or knee. The condition is diagnosed by presence of urate crystals in aspirates of joint fluid (38). Colchicine and non-steroidal anti-inflammatory drugs are used to treat acute attacks (39). Corticosteroids can also be used as an alternative.

Erythromelalgia

Erythromelalgia is a rare disease entity characterized by episodic burning pain, increased skin temperature, and bilateral redness of the extremities (40). It usually affects the feet and, to a lesser extent, the hands. Increased ambient temperature, fever, or exercise may induce symptoms. A dependent position may aggravate the disease. No symptoms or signs are present between attacks. Skin biopsy specimens show nonspecific changes and should not be routinely used. The paroxysmal nature of the disease, its aggravating factors, and the location of lesions may help differentiate erythromelalgia from cellulitis. Erythromelalgia may be primary or secondary. Myeloproliferative disorders have been particularly associated with the disease (41, 42). Several medications have been tried, with varying success. Some patients do not respond even to aspirin, which was once thought to be helpful in most cases (43). In cases of secondary erythromelalgia, treatment of the underlying disease may alleviate the symptoms.

Relapsing Polychondritis

Relapsing polychondritis is an uncommon disease that affects cartilaginous structures (44). Auricular chondritis is the most common manifestation, and it usually affects both ears. The acute inflammation may resemble cellulitis (45–47). However, a bacterial infection is usually unilateral and is associated with regional lymphadenopathy. In addition, relapsing polychondritis spares the ear lobe because this structure is not cartilaginous (48). Recurrent inflammation may result in auricular or saddle-nose deformity. Associated features include peripheral, nonerosive polyarthritis; episcleritis; keratitis or uveitis; and aortic valve insufficiency. These features support the diagnosis of relapsing polychondritis, which is primarily based on clinical criteria. Biopsy is indicated if the diagnosis is uncertain. Corticosteroids are usually effective, but immunosuppressive agents may be used in severe cases (49).

Carcinoma Erysipelatoides

Carcinoma erysipelatoides, also known as inflammatory carcinoma, is an uncommon form of skin metastasis. It develops when cancer cells invade the cutaneous lymph vessels (50, 51). It most commonly originates from breast

www.annals.org
carcinoma. Inflammatory breast cancer appears as an erythematous plaque on an enlarged breast. The absence of fever and leukocytosis should raise suspicion of a noninfectious process. Thus, if a suspected breast infection does not resolve with antibiotics, mammography and tissue biopsy should be done to rule out breast carcinoma. Because carcinoma erysipelatoides is a form of advanced cancer, treatment is based on managing the underlying malignancy.

**Familial Mediterranean Fever and Familial Hibernian Fever**

Familial Mediterranean fever is an autosomal recessive disease that primarily affects Jewish and Arab persons from the Mediterranean basin. It presents as acute self-limited episodes of fever accompanied by peritonitis, pleuritis, pericarditis, or synovitis (52, 53). Typically, the initial attack ensues in childhood or early adolescence. Erysipelas-like erythema is considered the most characteristic cutaneous manifestation of the disease. It consists of tender, erythematous, well-demarcated, warm, swollen areas with a diameter of 10 to 15 cm (54). These lesions usually occur below the knee, on the anterior leg or dorsum of the foot (unilaterally or symmetrically). The erythema subsides spontaneously within 24 to 48 hours as the acute attack resolves. The recurrent nature of the disease, a positive family history, and the coincidence of erythema with the acute attack help differentiate this entity from erysipelas. Nonetheless, skin lesions may sometimes occur without abdominal or chest pain. Colchicine is the drug of choice (55, 56).

Familial Hibernian fever is a rare distinct clinical entity that affects individuals of Irish ancestry (57). The characteristic erysipelas-like lesion may occur anywhere on the body, although the most common site is on a limb. It begins proximally and migrates distally during the course of the attack. The lesion (approximately 15 cm in diameter) is well-demarcated, erythematous, warm, and painful. Lesions do not respond to colchicine. Corticosteroids are usually effective, although symptoms may persist (58).

**Foreign-Body Reaction**

Some rare cases of adverse reactions to metallic implants have been described (59). Newer devices are associated with a lower rate of hypersensitivity reaction. Orthopedic implants, such as hip and knee prostheses, may cause noninfectious cellulitis-like erythema on the overlying skin. Sensitizing materials include nickel, chromium, and cobalt. Patch testing aids in the diagnosis. While a positive metal patch result is not definitive for an implant allergy, a negative result is more reliable for ruling out an implant allergy. If oral corticosteroids are ineffective, the prosthesis must be removed.

Mesothelial and the coincidence of erythema with the acute attack help differentiate this entity from erysipelas. Nonetheless, skin lesions may sometimes occur without abdominal or chest pain. Colchicine is the drug of choice (55, 56).

**DISEASES THAT UNCOMMONLY MASQUERADE AS INFECTIOUS CELLULITIS**

**Urticaria and Angioedema**

The pruritic lesions of urticaria vary in size. Uniform red giant urticaria lesions may masquerade as cellulitis. Angioedema consists of thicker plaques that result from massive transudation of fluid. If on the skin, angioedema lesions may also resemble infection (62). The transient character of the lesion, the associated pruritus, and a history of exposure to a precipitating factor aid in the differential diagnosis. Prevention of exposure to implicated agents and use of mast cell–stabilizing agents, such as ketotifen, are of paramount importance. For active lesions, oral antihistamines are used. Doxepin, a tricyclic antidepressant with H1-blocking properties, is useful for chronic urticaria (63).

**Follicular Occlusion Triad**

Hidradenitis suppurativa, acne conglobata, and dissecting cellulitis of the scalp constitute the follicular occlusion triad (64). These entities may rarely present simultaneously in the same patient and may resemble cellulitis. Dissecting cellulitis of the scalp can occur independently of the triad. This condition, also called perifolliculitis capsitis abscedens et suffodiens, is characterized by recurrent, painful, fluctuant dermal and subcutaneous nodules; scarring; and alopecia (65). It is clearly an inflammatory process that can be treated with retinoids, although antibiotics and corticosteroids have also been used successfully (66, 67).

**Lymphedema**

Lymphedema is characterized by nonpitting edema of an extremity (68). If it also appears with concomitant erythema and induration, it could masquerade as infectious cellulitis. The absence of fever or absence of response to antibiotics helps differentiate this condition from infectious disorders. Nonetheless, lymphedema itself may often be complicated by infection, even recurrently. Lymphangiography will clarify the diagnosis in uncertain cases (69). Treatment includes low-stretch compression garments and other mechanical means of reducing interstitial fluid accumulation (70). Antibiotics are used in cases of superinfection. Surgical treatment is reserved for severe cases, although its effectiveness is often questionable.

Postsurgical lymphedema of the breast has been used after mastectomy, excisional biopsy, or axillary lymph node excision (71, 72). Skin biopsy is occasionally required to rule out malignancy because the condition may also masquerade as carcinoma erysipelatoides. No specific treatment is required, and the condition frequently subsides spontaneously.

**Lupus Erythematosus**

Cutaneous lupus erythematosus can be classified into 3 forms: acute, subacute, and chronic or discoid lupus (73, 74). Lupus lesions are characteristically photosensitive. Dermatologic manifestations are also evident in most pa-
tients with systemic lupus erythematosus. Acute cutaneous
lupus erythematosus is manifested by papular, pruritic le-
sions on sun-exposed areas that range in color from ery-
thematosus to violaceous. These lesions may sometimes lead
to an erroneous diagnosis of infectious cellulitis. Acute cu-
taneous lupus erythematosus may involve fine scaling but
not atrophy. Disease activity may wax and wane in parallel
with underlying systemic lupus activity. Skin biopsy leads
to the correct diagnosis. In subacute cutaneous lupus ery-
thematosus, the appearance of the lesions ranges from that
of the acute butterfly rash to that of chronic discoid le-
sions. Lesions are hyperkeratotic with adherent scaling and
thus more closely resemble psoriasis.

Avoidance of sun exposure and use of sunscreens are
important measures for preventing the disease. Treatment
involves topical corticosteroids (75). Antimalarial agents
should be used for nonresponding lesions (76). Systemic
corticosteroids and immunosuppressants are reserved for
severe bullous lesions (77).

Sarcoidosis

The dermatologic manifestations of sarcoidosis include
the characteristic granulomas, as well as nonspecific lesions
such as erythema nodosum (78). Some atypical lesions may
resemble cellulitis because they manifest as indurated ery-
thematosus plaques associated with edema and pain (79).
The associated systemic findings, such as pulmonary in-
volve ment, lymphadenopathy, and uveitis, help establish
the correct diagnosis. Serum angiotensin-converting en-
zyme levels are useful, although not specific. Another help-
ful clue is the presence of skin lesions in the site of old
scars. Skin biopsy remains the primary diagnostic tool.
Pharmacologic treatment is usually reserved for severe sys-
temic disease and not for isolated skin manifestations.
Nonetheless, chronic cutaneous lesions, which may lead to
scarring, or widespread skin involvement should be treated
with corticosteroids (80).

Polyarteritis Nodosa

Polyarteritis nodosa is a multisystemic, necrotizing
form of vasculitis (81). Subcutaneous, inflammatory,
bright red to bluish nodules (<2 cm in diameter) that
follow the course of involved arteries are the characteristic
feature. They usually occur on the lower extremities and
are often bilateral. They become confluent to form painful
subcutaneous plaques that may resemble cellulitis. Ulcers
may result from ischemia. A cutaneous form of the disease
presents with the dermatologic lesions but without sys-
temic organ involvement (82, 83). Corticosteroids are used
to treat cutaneous and systemic polyarteritis nodosa. Cy-
clophosphamide is used in resistant cases or for its steroid-
sparing properties (84). Twenty percent of cases are asso-
ciated with hepatitis B antigenemia. Antiviral therapy is
beneficial for hepatitis-associated disease because immuno-
suppressive therapy may enhance viral replication (85).

Erythema Nodosum

Erythema nodosum is the most common form of pan-
niculitis. It usually consists of raised, painful, bilateral, ten-
der lesions that are frequently located over both shins but
may also occur on the knees, thighs, or arms (86). Some-
times, erythema nodosum may present as a large solitary
erythematous lesion. In addition, the typical erythema no-
dosum lesions may coalesce and thereby resemble infec-
tious cellulitis. The lesions resolve spontaneously in 4 to 6
weeks but may recur depending on the underlying illness.
Skin biopsy reveals septal panniculitis. Erythema nodosum
can be caused by several systemic disorders (87), such as
sarcoidosis, inflammatory bowel disease, and the Behçet
syndrome. It has also been attributed to medication use
and several infectious diseases (88, 89). Nonsteroidal anti-
inflammatory agents in full doses are usually effective. Cor-
ticosteroids can be used for severe cases if not contraindi-
cated by an underlying disease (90).

Lipodermatosclerosis

Lipodermatosclerosis, a form of panniculitis, was for-
merly called chronic indurated cellulitis and hypodermitis
sclerodermaformis. It usually affects middle-aged women
and is associated with venous insufficiency (91). The acute
form of the disease may masquerade as cellulitis. It presents
as a painful, erythematous, indurated, somewhat edema-
tous area in the medial aspect of the leg. It may extend to
the ankles and pretibial areas. The condition usually lasts
a few months but can persist for more than a year. Superim-
posed infectious cellulitis may occur and aggravate the clin-
cal manifestations of lipodermatosclerosis (92). Compres-
sion therapy, which reduces venous hypertension and fluid
extravasation, is useful (93). In addition, the lesions re-
spond favorably to stanozolol (94).

Morphea

Morphea, also known as localized scleroderma, is a
type of localized cutaneous sclerosis. These plaques are ini-
ially violaceous and then become ivory-colored (95). If
rapid in onset, the plaques may be erythematous. However,
the evolving changes and the associated induration help to
differentiate these lesions from infectious cellulitis. Treat-
ment with intralesional steroids or d-penicillamine may be
effective (96). The differential diagnosis should also in-
clude eosinophilic fasciitis and the eosinophilia–myalgia
syndrome, which may also masquerade as infectious cellu-
litis.

Other Forms of Panniculitis

Several physical agents, such as cold, blunt trauma,
and chemical materials injected subcutaneously (97), may
elicit panniculitis. Postirradiation pseudosclerodermatous
panniculitis is an unusual variant that results from mega-
voltage radiation therapy (98, 99). The differential diagno-
sis, which includes metastatic disease, infectious cellulitis,
or connective tissue disease, should be based on pathologic
findings.

Pancreatic disease, either inflammatory or neoplastic,
may lead to panniculitis presenting as tender, erythematous nodules. The lesions are located on the pretibial regions, thighs, or buttocks and occasionally discharge a yellowish oily substance. Treatment is directed at the underlying pancreatic disorder (100).

Lupus panniculitis consists of firm, well-demarcated plaques or nodules most commonly located on the face and upper extremities (101). Their diameter ranges from 1 to several centimeters. Results of the antinuclear antibody test are usually positive, although other signs of systemic lupus may be misleadingly absent. Patients should avoid sun exposure. Antimalarial agents or corticosteroids are usually effective. Immunosuppressive agents are used for resistant cases (102).

$\alpha_1$-Antitrypsin deficiency may present as cellulitis-like areas or red, tender nodules on the trunk and proximal extremities, often precipitated by trauma. Other signs of the disease, such as panacinar emphysema, noninfectious hepatitis, and cirrhosis, should suggest the diagnosis (103). Protein electrophoresis reveals low levels of $\alpha_1$-antitrypsin. Some patients respond to dapsone or $\alpha_1$-protease inhibitor concentrate (104).

Other forms of panniculitis, such as Weber–Christian disease, cytophagic histiocytic panniculitis, post-steroid panniculitis, and nodular panniculitis, may also uncommonly be confused with infectious cellulitis. For all the causes of panniculitis mentioned, biopsy can confirm the diagnosis. Because the inflammation occurs in the subcutaneous tissue, a deep excisional biopsy to the fascia rather than punch biopsy should be performed.

Lymphoma

Non-Hodgkin lymphomas and, to a lesser degree, Hodgkin disease can present with skin manifestations (105, 106). In rare cases lymphoma presents as cellulitis, usually diagnosed after failure of conventional antimicrobial therapy (107). Persisting fever or generalized lymphadenopathy may suggest the diagnosis. The Sézary syndrome is a form of cutaneous lymphoma characterized by generalized erythroderma (108). Extranodal natural killer/T-cell lymphoma, nasal type, causes the syndrome of midline granuloma, which may resemble facial cellulitis (109). Diagnosis of lymphoma always requires histologic confirmation. Localized disease should be treated with x-ray or electron-beam therapy (110). For extracutaneous disease, various chemotherapeutic agents have been used.

Leukemia

T-cell prolymphocytic leukemia is a rare chronic lymphoproliferative disease characterized by an aggressive clinical course. The principal disease characteristics are organomegaly, an elevated lymphocyte count, and dermatologic manifestations (diffuse erythema, infiltration localized to the face and ears, and skin nodules) (111). The condition sometimes mimics cellulitis (112). Other forms of leukemia may present with various skin lesions (including erythroderma) but are rarely misdiagnosed as cellulitis. Skin biopsy confirms the clinical suspicion. Cytotoxic chemotherapy is used to treat the disease.

Paget Disease

Paget disease of the breast constitutes the cutaneous manifestation of an underlying breast ductal carcinoma (113, 114). The disease consists of a rather sharply demarcated, unilateral eczematoid lesion affecting the nipple or areola. It is also associated with edema and hyperemia, thus mimicking infection. Eczematous dermatitis of the nipples, which is much more common, almost invariably appears bilaterally and responds to topical corticosteroids. Breast-conserving surgery followed by radiation therapy has excellent results in patients with limited underlying malignancy (115).

Extramammary Paget disease is a rare cutaneous adenocarcinoma that primarily affects the anogenital area. The disease appears as an erythematosus, eczematoid plaque, often associated with scaling. It is clinically and histologically similar to Paget disease of the breast. It may also be misdiagnosed as infectious cellulitis. The disease may be associated with a synchronous malignancy of the breast, lower gastrointestinal tract, urinary tract, or female genital tract (116). Surgical resection is recommended (117).

Glucagonoma

Glucagonoma, a tumor of the pancreas that is almost always malignant, presents with diabetes mellitus, diarrhea, and weight loss. It also causes characteristic necrotic migratory erythema. The rash begins as an erythematous area and gradually spreads; after central crusting occurs, the lesions heal. At the site of the initial erythema, hyperpigmented lesions remain. It usually affects intertriginous, perioral, and perigenital areas. The erythema may be the only presenting sign of the underlying malignancy (118). The rash responds poorly to therapy. Zinc supplementation and infusion of amino acids and essential fatty acids diminish its severity (119). Glucagonoma is treated by surgical resection in patients without widespread hepatic metastasis (120).

Calciphylaxis

Calciphylaxis primarily affects diabetic patients with end-stage renal disease and hyperparathyroidism who are receiving renal replacement therapy. Its pathophysiologic basis is widespread metastatic calcification leading to small-vessel vasculopathy. At an early stage, it presents with non-ulcerating plaques in the calves and is easily confused with cellulitis (121). The lesions eventually become necrotic and painful ulcers develop. A history of renal disease and the evolution of the lesions help diagnose calciphylaxis, which is managed by treatment of the renal failure and debridement of any necrotic tissue (122). Subtotal parathyroidectomy may be helpful (123).

Compartment Syndrome

Acute compartment syndrome is caused by increased pressure in an enclosed osseofascial space (124). It usually
affects the anterior tibial compartment. Common causes include open or closed fractures, soft-tissue injury, extrinsic compression, reperfusion injury, and strenuous exercise. Pain out of proportion to the sustained injury is a cardinal feature. Cutaneous manifestations are occasionally present and include dusky redness of the skin overlaying the compartment. Rarely, the lesions may resemble cellulitis. Cases of compartment syndrome unrelated to an obvious injury may challenge the clinician (125). The condition is diagnosed by measuring the compartment pressure. Full-blown cases of the syndrome necessitate emergency fasciotomy (126).

CONCLUSION

Physicians challenged by a case of cellulitis that does not respond to conventional antimicrobial agents should promptly consider a noninfectious cause of cellulitis. A thorough history and a complete physical examination are the major tools in a productive differential diagnosis. Chronic lesions suggest the possibility of a noninfectious cause; in contrast, acute lesions are usually caused by an infectious agent.

Routine and special laboratory tests may be done to confirm the postulated diagnosis. In many cases, cutaneous biopsy specimens examined by an experienced pathologist may be needed to identify the correct diagnosis. Skin biopsy may be performed at an earlier stage before advanced diagnostic tests are done. An appropriate biopsy specimen should be obtained. Special stains are sometimes required to rule out lymphomatous disease. In addition, mycobacterial and fungal stains may be used to exclude an atypical infectious agent. Cultures for common bacteria, mycobacteria, and fungi should also be obtained.

From Alfa HealthCare, Athens, Greece, and Tufts University School of Medicine, Boston, Massachusetts.

Acknowledgment: The authors thank Dr. Sofia K. Kasiakou for critical review of the manuscript.

Requests for Single Reprints: Matthew E. Falagas, MD, MSc, Alfa HealthCare, 9 Neapoleos Street, 151 23 Marousi, Athens, Greece; e-mail, matthew.falagas@tufts.edu.

Current author addresses are available at www.annals.org.

References


Current Author Addresses: Drs. Falagas and Vergidis: Alfa HealthCare, 9 Neapoleos Street, 151 23 Marousi, Athens, Greece.