Seminars in Cutaneous Medicine and Surgery

Approach to the Patient With Presumed Cellulitis

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Dermatologists frequently are consulted in the evaluation and management of the patient with cellulitic-appearing skin. For routine cellulitis, the clinical presentation and patient symptoms are usually sufficient for an accurate diagnosis. However, when the clinical presentation is somewhat atypical, or if the patient fails to respond to appropriate therapy for cellulitis because of routine bacterial pathogens, the differential diagnosis should be rapidly expanded. We discuss the approach to the patient with presumed cellulitis, with an emphasis on the differential diagnosis of cellulitis in both the immunocompetent and immunucompromised patient.
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A 53-year-old woman with a history of recurrent breast cancer diagnosed 2 years before presentation and treated with radiation and chemotherapy (docetaxel, anastrozole, exemestane, gemcitabine) most recently 6 months before presentation was admitted for 3 weeks of worsening chest wall pain and a rash over her mastectomy scar. Despite 5 days of empiric antibiotic therapy with doxycycline and vancomycin, the chest wall erythema and pain were increasing. A dermatology consultation was called. An ulceration and surrounding erythematous papules were concentrated over the mastectomy scar with ill-defined erythematous patches that extended to the upper chest bilaterally (Fig. 1). At the time of dermatologic evaluation, the patient was afebrile. Laboratory tests showed an increased white blood cell count of 13.5 $\times$ 10^9/L (normal range, 3.4-10 $\times$ 10^9/L), with a neutrophilia (9.9 10^9/L; normal range, 1.8-6.8 $\times$ 10^9/L) and eosinophilia (0.53 $\times$ 10^9/L; normal range, 0.0-0.4 $\times$ 10^9/L). A complete metabolic panel and liver function tests were within normal limits. Urine and blood cultures were negative. A computed tomography of the chest, abdomen, and pelvis showed skin thickening and subcutaneous edema in the region of the right mastectomy without radiologic evidence of metastatic disease. Biopsy of an erythematous papule showed a sparse perivascular and interstitial dermatitis, suggestive of cellulitis, and telangiectasia and scattered enlarged mesenchymal cells, characteristic of radiation changes.

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Clinical Problem

Dermatologists frequently are consulted in the evaluation and management of the patient with cellulitic-appearing skin. Although the dermatologist may be consulted early on in the patient's course, more often a dermatology consult is requested when a patient fails to respond to treatment. It is at this juncture that the dermatologist's expertise uncovers an alternate, often course-altering, diagnosis.

Cellulitis is an infection of the dermis and subcutis that produces warm, red, tender, poorly demarcated areas of skin. When severe, the infection can cause edema, vesicles, bullae, pustules, necrosis, and lymphangitis.[1] *Erysipelas* is a term used to describe a superficial cellulitis, most often of the face, that extensively involves the lymphatics, creating raised, firm, shiny plaques.[2,3] Signs and symptoms associated with both cellulitis and erysipelas may include malaise, fever, chills, and toxicity.

In immunocompetent adults, cellulitis is most often caused by *Staphylococcus aureus* (either methicillin sensitive *S. aureus* (MRSA) or methicillin resistant *S. aureus* (MSSA)) or *Streptococcus pyogenes* and is found on the lower extremities.[1-3] In pediatric patients, cellulitis is often caused by *S. aureus* and, with the success of the *Haemophilus influenzae* type b vaccination efforts, less frequently *H. influenzae*.[1,2] Children most often present with lesions of the face and neck but can also develop perianal cellulitis caused by group A streptococci.[1,2] Perianal cellulitis tends to have a more alarming presentation with perianal erythema and pruritus, purulent secretions,

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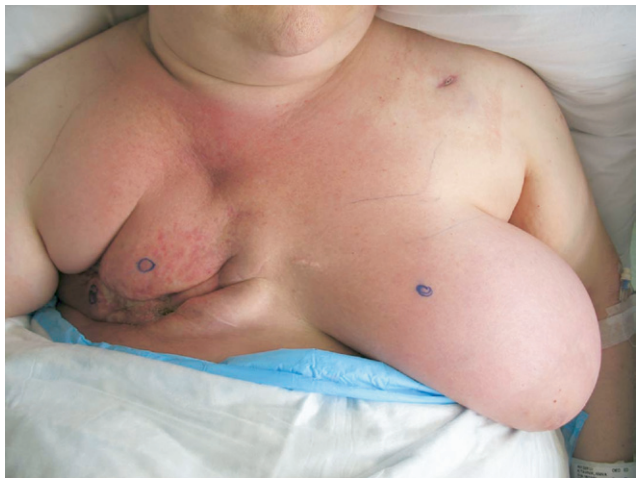

Figure 1 Erythematous papules concentrated over mastectomy scar overlying ill-defined erythematous patches that extend to upper chest bilaterally. Note area of ulceration directly over the mastectomy scar.

anal fissures and rectal bleeding.[2] Periorbital cellulitis, which affects the periocular skin and tissue anterior to the orbital septum, should be distinguished from orbital cellulitis, which spans the tissues beyond the septum and has the potential to cause diminished vision and cavernous-sinus thrombosis.[2] Multiorganism cellulitis (anaerobes and Gram-negative aerobes) tends to occur in patients with chronic ulcers secondary to diabetes, venous insufficiency, or pressure (decubitus ulcers). Cellulitis accompanied by crepitus or a thin, gray-brown, malodorous discharge should raise concern for anaerobic cellulitis, a necrotizing infection that can progress to myonecrosis.[1,2] Usually caused by *Clostridium perfringens*, anaerobic cellulitis also may be caused by non-sporulating anaerobes such as *bacteriodes*, *peptostreptococci*, *peptococci*, and *Prevotella*.[1,2] Anaerobic cellulitis usually arises in dirty wounds, most often in patients with underlying peripheral vascular disease or diabetes.[1] These infections require surgical debridement and antibiotics.[1,2]

Small breaks in the skin, as can occur with minor trauma, injection drug use ("skin popping"), body piercing, or animal or human bites, serve as portals of entry for bacteria and skin infection. Tinea pedis is a common concomitant fungal infection that predisposes to bacterial cellulitis. Recurrent cellulitis typically occurs secondary to damaged blood vessels and/or lymphatics due to prior episodes of cellulitis, peripheral vascular disease, intravenous drug abuse, lymph node dissection (including mastectomy or lumpectomy with axillary node dissection for breast cancer), radiation therapy, liposuction, or vein harvest for coronary artery bypass surgery.[1,2] Hematogenous spread of bacteria from other sites to the skin occurs most commonly in the immunosuppressed patient.[1] Lymphadenitis, subacute bacterial endocarditis, glomerulonephritis, and, with recurrent cellulitis, elephantiasis verrucosa nostra are potential, but uncommon, complications of cellulitis.[1]

Evaluation

The evaluation of the patient who presents with red, hot, tender skin begins with a complete history and physical examination. For routine cellulitis, the clinical presentation and patient symptom complex are usually sufficient for an accurate diagnosis. When the clinical presentation is somewhat atypical, or if the patient fails to respond to appropriate therapy for cellulitis due to routine bacterial pathogens, the differential diagnosis should be rapidly expanded. Important information to elicit from the patient is the onset and duration of the eruption, inciting or relieving factors, whether this is a first or recurrent episode, symptoms such as pain or pruritus, and the presence of associated symptoms (eg, arthritis, diarrhea, cough or headache). The acute onset of erythema, tenderness, and edema with fever and chills implies an infectious process whereas erythema, edema, and severe pruritus without associated fever or chills would suggest, for example, a contact dermatitis or an insect bite reaction. The patient's past medical history should be reviewed in detail. Certain underling conditions predispose patients to cellulitis. For instance, cyclic neutropenia, a rare neutrophil synthesis disorder that results in recurrent, regular episodes of neutropenia, is often accompanied by fever, oral ulcers, malaise, and skin and upper respiratory infections, including cellulitis.[4] The presence of absolute or relative immunosuppression (eg, diabetes mellitus, HIV infection, chronic systemic corticosteroid use, leukemia, neutropenia, biologic therapies, stem cell or solid organ transplant) should raise concern for unusual or opportunistic infections. A family history of "recurrent cellulitis" might suggest a hereditary condition such as Familial Mediterranean Fever. The presence of a known underlying malignancy may raise concern for carcinoma erysipeloides. A social history, including travel, hobbies, pets, and animal exposures can help narrow an otherwise broad differential diagnosis. A complete drug history of both prescription and over the counter medications should be obtained.

The physical examination begins with a global assessment of the patient (well appearing, acutely, or chronically ill; intubated in the intensive care unit or on the oncology floor). Although not always present, a fever implies infection or a systemic inflammatory process. The fever pattern should be scrutinized (eg, diurnal swings would suggest Still's disease). Tachycardia might indicate severe pain in the patient who cannot articulate this symptom. A complete skin examination, including lymph node examination, should be performed, as clues to the underlying diagnosis might lie outside of the area in question. Lymph node involvement most often suggests an infectious, inflammatory, or neoplastic process. When focusing on the affected area, color, surface change, primary morphology, secondary changes, and distribution of erythema are all key features to note. For example, a tender and swollen extremity with minimal to no overlying erythema implies a process affecting deeper tissues (e.g., pyomyositis or diabetic skeletal muscle infarction). In a toxic-appearing patient with severe pain, rapidly advancing erythema, and overlying skin necrosis, necrotizing fasciitis should be immediately ruled out.

Laboratory tests should include a complete blood count with differential, liver function tests, and a chemistry panel. More specific laboratory test should be ordered based on the clinical picture and the differential diagnosis. In routine cellulitis, patients often have sterile blood cultures and normal or slightly increased leukocyte counts (unless the bone marrow is compromised by chemotherapy, malignancy, or infection). Blood cultures and cultures of bullae, pustules, or ulcers should be obtained in patients who have cellulitis.

For routine cellulitis, skin biopsy is not necessary. When performed, a skin biopsy typically shows a mixed lymphoneutrophilic dermal infiltrate with or without extension into the subcutaneous tissue. Dilated blood vessels and lymphatics can be identified with dermal edema. When severe, dermal edema can result in the formation of subepidermal bullae.[1] When an infectious, especially nonbacterial, etiology is suspected, skin biopsy for histopathologic evaluation (routine hematoxylin-and-eosin as well as special stains for organisms) and culture (for bacteria, fungi, and mycobacteria) should be performed. In addition, a skin biopsy should be performed in all cases of cellulitis in an immunocompromised patient. Skin biopsy should also be performed when the differential diagnosis includes noninfectious mimickers of cellulitis.

Imaging can be helpful in distinguishing cellulitis from more severe infections. Radiograph and computed tomography imaging can reveal underlying osteomyelitis. Magnetic resonance imaging (MRI) can delineate the extent of infection and help to distinguish severe cellulitis from pyomyositis or necrotizing fasciitis. Ultrasonography and MRI can identify foci of accumulated pus for aspiration.[2]

Differential Diagnosis

The differential diagnosis of a cellulitis- or erysipelas-like eruption is broad. Infectious conditions in the differential diagnosis of routine cellulitis or erysipelas are listed in Table 1. The list of organisms reported to cause cellulitis or erysipelas in the immunocompromised host is listed in Table 2. Table 3 discusses the differential diagnosis of noninfectious mimickers of cellulitis or erysipelas. Although space constraints do not allow for discussion all of the entities listed in these tables, conditions that are newly reported, those of particular interest to dermatologists, and those with unusual or special features are discussed in more detail.

Infectious Differential Diagnosis of Cellulitis or Erysipelas in the Immunocompetent Host (Table 1)

Specific Entities

Contiguous spread of subcutaneous infections. Contiguous spread of subcutaneous infections to the skin can result in cellulitis. For example, a perforating sigmoid diverticula has presented as left thigh cellulitis.[5] Cellulitis can be a postoperative complication resulting from organisms found in absorbable implanted devices, such as pelvic mesh slings.[6] Occasionally, cellulitis may be caused by the spread of subjacent osteomyelitis.[2]

Dental sinus or abscess. A dental sinus or abscess can present with facial cellulitis overlying the involved tooth or sinus. The infection is often painful and readily found radiographically. In the edentulous patient with facial cellulitis, a high index of suspicion is needed to look for an abscess surrounding retained dental root fragments.

Hematogenous dissemination. Cellulitis can rarely be caused by hematogenous dissemination from an underlying infection. Systemic infection with *Neisseria meningitidis*,[7] brucellosis,[8,9] *Pseudomonas aeruginosa*,[10] and *Legionella*[11] have all been reported to have an associated cellulitis or erysipelas caused by metastatic infection.

Pyomyositis. Pyomyositis is a primary suppurative infection of skeletal muscle, usually due to *S. aureus*. Predisposing conditions include trauma, HIV infection, malnutrition, diabetes, parasitic infection, travel or emigration from tropical areas, hematologic malignancy, and intravenous drug use. Patients with pyomyositis most often present with severe pain and induration of the affected area with minimal to no overlying skin changes. A muscle of the pelvic girdle or lower extremity is most often affected. Blood cultures are positive in

Table 1 Infectious Differential Diagnosis of Cellulitis or Erysipelas in the Immunocompetent Host

- Specific diagnoses
  - Contiguous spread of subcutaneous infections[5,6]
  - Dental sinus or abscess
  - Hematogenous dissemination from an internal source[7,8,10,11]
  - Phlegmon[61]
  - Pyomyositis[12]
  - Necrotizing fasciitis[2]
- Specific infections
  - Bacterial
    - Erysipeloid (*Erysipelothrix rhusipathiae*)[16]
    - Erythema migrans (*Borrelia borgdorferi*)[18]
    - Cutaneous anthrax[2]
    - *Vibrio Vulnificus*
    - *Aeromonas hydrophilia*
  - Viral
    - Parvovirus B-19[62]
    - Prevesicular herpes zoster[63]
  - Fungal
    - Dermatophytosis[64]/dermatophytid[65]
  - Parasitic
    - Onchocerciasis (erysipelas de la costa)[66]
    - Leishmaniasis[67,68]
    - *Dermatobia hominis*[58]
  - Mycobacterial
    - *Mycobacterium kansasii*[69]
    - *Mycobacterium chelonae*[70]
    - *Mycobacterium abscessus*[71]
  - Post-Vaccination (inoculations)
    - Vaccinia (preseptal cellulitis)[72]
    - *H. influenza B* (periorbital and orbital cellulitis)[73]

Table 2 Infectious Differential Diagnosis of Cellulitis or Erysipelas in the Immunocompromised Host

Bacterial
Bacillus anthracis
Bartonella
Campylobacter jejuni
Cunninghamella
Erysipelothrix insidiosa
Escherichia coli
Group G streptococcus
Helicobacter cinaedi
Haemophilus influenzae
Legionella micdadei
Moraxella
Morganella morganii
Nocardia asteroides
Prevotella
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus, S. epidermidis
Streptococcus iniae, S. pneumoniae, S. zooepidemicus
Vibrio vulnificus
Yersinia enterolitica
Xanthomonas maltophilia
Viral
Herpes simples virus
Cytomegalovirus[74]
Fungal
Alternaria
Aspergillus
Bipolares hawaiiensis
Candida
Cryptococcus neoformans[75]
Exophiala jeanselmei, E. spinifera, E. pisciphera, E. castellani
Exserohilum rostratum
Fonsacaea pedrosoi
Fusarium solanae
Histoplasmosis
Mucormycosis[76]
Paecilomyces
Phaeohyphomycosis
Phialophora parastica
Prototheocosis
Pseudoallescheria boydii
Rhizopus
Sporothrix schenckii[77]
Trichophyton rubrum
Trichosporon cutaneum
Parasitic
Acanthamoeba
Dermatobia hominis (myiasis)
Onchocercosis
Trypanosoma cruzi[78]
Mycobacterial
Mycobacterium abscessus
Mycobacterium avium intracellulare
Mycobacterium bovis
Mycobacterium chelonae
Mycobacterium fortuitum
Mycobacterium haemophilium[79]
Mycobacterium kansasii
Mycobacterium szulgai
Mycobacterium thermoresistible
Mycobacterium tuberculosis

Data adapted from *A Clinician's Guide to Dermatologic Differential Diagnosis.*[61]

up to 38% of patients.[12] Patients with pyomyositis are initially believed to have cellulitis; therefore, the diagnosis is usually considered when patients fail to respond to appropriate treatment for cellulitis. Diagnosis requires a high level of suspicion and is confirmed by imaging (magnetic resonance imaging is the most useful). Treatment requires intravenous antibiotics and drainage of the abscess.[12]

Necrotizing fasciitis (NF). NF is a rapidly progressive infection of the subcutaneous tissues that most frequently involves the abdomen, extremities and perineum.[13] Three types exist: (1) polymicrobial (nongroup A streptococci, *Escheria*, *Enterobacter, Klebsiella, Proteus, Bacteroides, Fusobacterium, Peptococcus, Clostridium*); (2) group A beta hemolytic streptococcus; and (3) marine *Vibrio.*[13] Risk factors for the development of necrotizing fasciitis include diabetes mellitus, obesity, immunosuppression, alcoholism, intravenous drug use, smoking, malnutrition, and peripheral vascular disease.[13,14]

Clinically, patients may present with flu-like complaints and erythematous, edematous, warm, painful skin that is often confused with cellulitis.[13-15] Blistering and crepitus may be present. A classic clinical feature is pain out of proportion to the clinical findings.[13-15] Woody induration of the subcutaneous tissue and progression to more pronounced illness follows, with fever, hypotension, and tachycardia.[15] Rapid spread of the involved areas ensues, despite antibiotic therapy.[13,14] The final development of malodorous, hemorrhagic bullae is a poor-prognostic indicator seen in up to 30% of patients.[13,14] Death from sepsis-induced multi-organ failure occurs in 16% to 24% of patients.[13-15]

The diagnosis of necrotizing fasciitis requires a high index of suspicion. Magnetic resonance imaging is best for delineating the extent of infection and ruling out other potential etiologies of the clinical findings.[15] On operative examination, the easy separation of involved from surrounding tissue, the presence of a thin, brown exudate, and the absence of bleeding are also helpful diagnostic signs.[13,15]

Treatment of necrotizing fasciitis includes rapid initiation of broad-spectrum antibiotics and surgical debridement of all necrotic tissue.[13-15] Fluid resuscitation and monitoring for potential panniculitis-induced hypocalcemia should take place.[13] Adjunctive therapies reported include hyperbaric oxygen, anticoagulant therapy, and intravenous immune globulin.[13-15]

Specific Infections: Bacterial

Erysipeloid (Erysipelothrix rhusipathiae). *Erysipelothrix rusiopathiae* is a Gram-positive bacillus that causes erysipeloid, an acute skin infection clinically characterized by an erythematous to violaceous painful plaque usually on the hand.[16,17] The skin findings may be accompanied by fever,

Table 3 Differential Diagnosis of Cellulitis or Erysipelas: Non-infectious

- Inflammatory
  - Autoinflammatory syndromes
    - Familial Mediterranean fever[20,21]
    - Tumor necrosis factor receptor-associated periodic syndrome[80]
  - Panniculitis
    - Erythema nodosum
    - Subcutaneous fat necrosis of the newborn[81]
    - Cold panniculitis[24]
    - Alpha-1 antitrypsin deficiency panniculitis[25,26]
    - Lipodermatosclerosis[42]
    - Lupus panniculitis
    - Pancreatic panniculitis
  - Neutrophilic diseases
    - Sweet's syndrome[27]
    - Neutrophilic eccrine hidradenitis[28]
  - Connective tissue diseases
    - Scleroderma (acute edematous phase)[61]
    - Intravascular/lymphatic histiocytosis associated with rheumatoid arthritis[82]
    - Relapsing polychondritis
  - Inflammatory bowel diseases
    - Metastatic Crohns disease[83-85]
  - *Other inflammatory diseases*
    - Well's syndrome[33]
    - Giant urticaria/angioedema[3]
    - Autoerythrocyte sensitization syndrome (painful bruising syndrome)[86]
    - Scleredema
    - Nephrotic crisis[87]
    - Erythromelalgia[88]
    - Erythema overlying infection or inflammation of underlying structure (erythema of flank overlying area of bowel perforation) (L.P.F., personal observation)
    - Sarcoidosis[61]
    - Kawasaki disease[89]
    - Compartment syndrome[90]
    - Following breast surgery[43-45]
    - Periductal mastitis[91]
- Neoplastic
  - Primary
    - Inflammatory breast carcinoma[91]
    - Cutaneous angiosarcoma[92]
    - Retinoblastoma (orbital cellulitis)[93]
    - Malignant melanoma (orbital cellulitis)[94]
    - Multiple myeloma[61]
    - Peripheral T-cell lymphoma[95]
    - NK/T cell lymphoma[96]
    - T-cell prolymphocytic leukemia[34]
    - Primary skeletal muscle lymphoma[97]
    - Pagets disease of breast
    - Extramammary Pagets disease
  - Metastatic (carcinoma erysipeloides)
  - Metastatic malignant melanoma[98]
    - Ovarian carcinoma[38]
    - Tonsillar carcinoma[38]
    - Gastric carcinoma[99-103]
    - Uterine carcinoma[104]
    - Breast carcinoma[105]
    - Lung carcinoma[37]
    - Colon carcinoma[106]
    - Rectal carcinoma[38]
    - Pancreatic carcinoma[38]
    - Parotid carcinoma[38]
    - Squamous cell carcinoma (unknown origin)[107]
    - Genitourinary carcinoma[108]
    - Prostate carcinoma[109]
    - Anaplastic thyroid carcinoma[36]
    - Nasopharyngeal carcinoma[110]
- Vascular
  - Generalized acquired telangiectasia[61]
  - Calciphylaxis[40]
  - Leukocytoclastic vasculitis[111]
  - Deep vein thrombosis[3]
  - Superficial thrombophlebitis[3,61]
  - Venous insufficiency dermatitis[41]
  - Lymphedema[42,61]
  - Neonatal purpura fulminans[61]
- Hematologic
  - Sickle cell disease[112]
  - Hereditary Spherocytosis[113]
  - Cutaneous Graft-versus-Host Disease[46]
- Metabolic
  - Gout[2,3]
  - Diabetes mellitus[61]
  - Calcinosis cutis (in dermatomysitis)[61]
- Iatrogenic, Factitial, or Exogenous
  - Iatrogenic
    - Radiation dermatitis (L.P.F., personal observation)
    - Radiation recall[114]
  - Drug eruptions
  - Injection site reactions
    - Vitamin K reaction[61]
  - Fixed-drug eruption
    - Topotecan fixed-drug reaction[51]
    - Chlorambucil[90]
    - Furosemide[61]
    - L-asparaginase[61]
    - IL-2 therapy[115]
    - Paracetamol[49]
  - Gemcitabine[116]
  - Clopidogrel bisulfate (Systemic inflammatory response syndrome)[117]
  - Calcinosis cutis after calcium gluconate extravasation[118]
  - Coumadin necrosis (early)[61]
  - Pressure bullae
  - Coma bullae[61]
- Vaccinations
    - Diphtheria-tetanus-acellular pertussis (DPT)[53]
    - Well's syndrome after DPT[119]
  - Contact dermatitis
    - Contact dermatitis to underlying mesh/prosthesis
    - Irritant contact dermatitis[61]
    - Plant dermatitis (Rhus, other)
  - Foreign body
    - Orthopedic implants[120]
    - Milk injections[61]
    - Parafinoma
    - Silicone reaction/granuloma[54]
    - Factitial

Table 3 Continued

Occupational
High-pressure injection injury[55]
Toxic exposure
Mercury[56]
Ricin (in conjunction with *Enterococcus faecalis*)[121]
Infestations/bites/stings
Insect bite reaction[61]
Brown recluse spider bite
Black widow spider bite
Myiasis (*Dermatobia hominis*)[58-60]
Fish stings[61]
Centipede bite[61]

lymphadenopathy, lymphangitis, and arthralgias.[16,17] The organism has been associated with contact with infected animals, specifically farm animals, including fowl and fish.[16] Features that distinguish erysipeloid from classic staphylococcal or streptococcal cellulitis include severe pain, a lack of edema, and the violaceous color.[16] Although typically a localized infection, erysipeloid can present with a diffuse cutaneous form with satellite lesions as well as a rare systematized form that may lead to sepsis, endocarditis, and, rarely, glomerulonephritis and meningitis.[16,17] The systemic form rarely occurs following localized infection and is thought to correlate with hyaluronidase and neuraminidase production by the organism.[16] Although erysipeloid usually resolves spontaneously in three to four weeks, recurrences and chronic infection can occur; thus, antibiotic therapy with penicillin or cephalosporins is recommended.[16]

Erythema migrans. The bite of a *Borrelia*-infected *Ixodes* tick can produce expanding, warm patches of erythema that, in the absence of intervening rings of normal skin or central pallor, can resemble cellulitis. Most lesions lack central clearing, which when coupled with fever and other constitutional symptoms, leads to confusion with cellulitis.[18,19] Clues to distinguish erythema migrans include occurrence in the spring or summer, history of tick bite, recent travel to endemic areas, multiple annular lesions (some cases), and location of the lesions in areas that are atypical for cellulitis such as the back, groin, waist, popliteal fossa, and axilla.[18,19] The center of the lesion may contain vesicles, pustules, bullae, or necrosis making the lesion more difficult to distinguish from cellulitis. Microbiologic confirmation obtained via culture of a skin biopsy or aspiration of the leading edge of the lesion is only available in specialized laboratories.[19] If there is uncertainty, treatment with amoxicillin/clavulanate will cover staphylococci, streptococci, and *Borrelia burgdorferi*.[19]

Infectious Differential Diagnosis of Cellulitis or Erysipelas in the Immunocompromised Host (Table 2)

The immunosuppressed patient who presents with "cellulitis" requires special consideration. In addition to the conditions that typically mimic routine cellulitis in the immunocompetent host, unusual infectious etiologies should always be considered (Table 2). Biopsy of the skin for histopathologic evaluation (routine hematoxylin-and-eosin and special stains) and culture (for bacteria, fungi, and mycobacteria) should be performed. Broad-spectrum antimicrobials should be initiated until a specific infectious etiology is identified and antimicrobial therapy can be tailored appropriately.

Noninfectious Differential Diagnosis of Cellulitis or Erysipelas (Table 3)

Inflammatory

Autoinflammatory syndromes. The autoinflammatory syndromes are entities currently under intense investigation. This group includes Familial Mediterranean Fever, Hyper IgD syndrome, tumor necrosis factor receptor-associated periodic syndrome, Muckle-Wells syndrome, periodic fever with aphthous pharyngitis and adenitis, familial cold autoinflammatory/familial cold urticaria, and neonatal-onset multisystemic inflammatory disease. Familial Mediterranean Fever (FMF), an autosomal-recessively inherited disorder, causes recurrent attacks of fever and polyserositis, with erysipelas-like erythema of the lower extremity.[20,21] FMF is caused by mutation in the MEFV gene that encodes the protein pyrin or marenostrin, thought to be a leukocyte-specific inflammatory regulator.[22] The disease tends to affect Sephardic Jew, Armenians, Arabs, and Turks.[20,21] The characteristic skin lesion is a unilateral or bilateral, tender, well-demarcated, large, erythematous, hot, patch or plaque on the lower leg or foot.[20-22] Although multiple other lesions have been described in association with FMF, erysipelas-like erythema is the most notable.[20,21] Histologically, the lesions are nonspecific.[21] Tumor necrosis factor receptor-associated periodic syndrome has also been reported to have cellulitis- or erysipelas-like cutaneous manifestations.[22]

Panniculitis. There are several forms of panniculitis that can be confused with cellulitis or erysipelas. These include erythema nodosum, subcutaneous fat necrosis of the newborn,[23] cold panniculitis,[24] and alpha-1-antitrypsin deficiency panniculitis.[25,26] Erythema nodosum, one of the more common types of panniculitis, can present with a solitary tender red plaque. It may be accompanied by fever, malaise, leukocytosis, and an elevated erythrocyte sedimentation rate. This "cellulitis-like lesion" may over days be accompanied by multiple more discrete, red, tender, subcutaneous nodules or become bruise-like. These changes allow for recognition of typical erythema nodosum. Some confusion may exist if the cause of the erythema nodosum is streptococcal pharyngitis or pulmonary tuberculosis. Skin biopsy will confirm erythema nodosum and clarify the clinical situation.

Neutrophilic Diseases

Both Sweet's syndrome (acute febrile neutrophilic dermatosis)[27] and neutrophilic eccrine hidradenitis[28] have been reported to produce cellulitis- or erysipelas- like cutaneous lesions. Sweet's syndrome can resemble cellulitis when it involves the lower extremities or erysipelas when sharply demarcated lesions develop on the face. Most patients present

with leukocytosis, neutrophilia, and an elevated erythrocyte sedimentation rate or C-reactive protein.[27] Sweet's syndrome occurs in association with infections of the respiratory or gastrointestinal tract, vaccinations, inflammatory bowel disease, pregnancy, hematologic malignancy (most commonly acute myelogenous leukemia), solid organ malignancy, and medications.[27,29-31] Sweet's syndrome should be suspected in patients with acute myelogenous leukemia who present with fever and erythematous plaques unresponsive to antibiotics.[2,32]

Well's syndrome. Eosinophilic cellulitis, or Well's syndrome, consists of the acute onset of erythematous, swollen papules, and/or plaques most often on the extremities and trunk. The lesions appear urticarial or cellulitic in the acute phase and then fade over several days leaving indurated hyperpigmentation.[2,33] Well's syndrome is thought to represent a hypersensitivity reaction to a variety of possible triggers including insect bites, drugs, and infections.[2,33] Peripheral eosinophilia and dermal eosinophilic infiltration can help to distinguish Well's syndrome from routine cellulitis.[2,33]

Neoplastic

Leukemia/lymphoma. Skin involvement by leukemic cells is observed in <5% of B-cell leukemias and >10% of T-cell leukemias.[34] Presentation of both leukemia and lymphoma can include infiltrated, widespread erythema as well as erythematous papules, nodules and plaques.[34,35] These lesions have been confused with cellulitis and must be distinguished from true cellulitis, which can arise with increased frequency in an immunosuppressed patient with leukemia or lymphoma.[34,35] Biopsy with immunostaining will reveal the correct diagnosis.[34,35]

Carcinoma erysipeloides. Carcinoma erysipeloides describes the well-circumscribed, erythematous, warm, firm plaques on the skin that occur as a result of metastases to the skin from an underlying malignancy. This condition is most often seen in association with breast cancer, but has also been reported with multiple other internal malignancies (Table 3).[36-38] Carcinoma erysipeloides is often confused with cellulitis and can be distinguished via atypical location, and absence of pain, fever and neutrophilia.[37] Often the diagnosis is made when 'cellulitis' fails to respond to antibiotic therapy and a biopsy is performed.[37] Rarely, carcinoma erysipeloides can be the first presentation of an underlying malignancy.

Vascular

Calciphylaxis (calcific uremic arteriolopathy). Calciphylaxis is necrosis of the skin and underlying soft tissue that results from the ischemic changes of progressive vascular calcification.[39] It is associated with patients undergoing peritoneal or hemodialysis for end-stage renal disease.[40] Early lesions present abruptly as exquisitely painful dusky red or violaceous plaques that progress rapidly to ulceration and gangrene.[39,40] Many cases present with nonulcerated, tender, erythematous subcutaneous plaques in the lower extremities that may mimic cellulitis.[40] Proximal lesions of the lower abdomen or buttocks and ulceration are associated with a worse prognosis. Mortality results from sepsis, malnutrition or the discontinuation of dialysis.[39,40] Skin biopsy typically confirms the diagnosis but can cause ulceration and poor healing at the biopsy site.

Deep vein thrombosis (DVT). Patients with DVT most commonly present with unilateral lower-extremity erythema, warmth, and swelling. These symptoms may be accompanied by fever, leukocytosis, and pain of the lower extremity.[3] Differentiating a DVT from cellulitis may be difficult. A hypercoagulable history or a palpable cord may help in identifying a DVT.[3] Ultrasonography is, at minimum, needed to confirm the diagnosis.

Venous insufficiency/lipodermatosclerosis. Chronic venous stasis produces lower-extremity edema, erythema, and hyperpigmentation as well as ulceration and lipodermatosclerosis.[41] Venous hypertension results most often from reflux of blood through incompetent leg vein valves in the superficial and/or deep venous plexuses. This produces diminished blood return to the heart and increased venous pressures which acutely can result in one or two red legs. Often dermatologists are consulted to "rule-out cellulitis" in these patients. The bilateral nature of this condition, prominence over the medial malleoli, absence of fever and leukocytosis, and response to leg elevation and compression are clues to the cellulitis-like changes of peripheral vascular disease. Patients also may report symptoms of lower-extremity heaviness, aching, cramping, itching, and restlessness rather than fever and pain.[41] Lipodermatosclerosis describes thickened, shiny, erythematous, bound down, often painful, skin of the lower extremities. It has been associated with chronic venous insufficiency and recurrent bouts of cellulitis.[42] Histologically, it is marked by stasis dermatitis, panniculitis with septal thickening and fibrosis, and adipocyte necrosis with lipomembranous change. When viewed by a physician unfamiliar with this condition, lipodermatosclerosis can easily be confused with cellulitis.

Postsurgical lymphedema of the breast. Lymphedema of the breast after surgery for breast carcinoma, partial mastectomy, breast biopsy, or axillary lymph node surgery typically presents as a warm, erythematous, edematous patch or plaque with "peau d'orange" surface change on the breast and/or areola.[43-45] The skin changes typically appear 1 to 2 weeks after the procedure, closely resemble infectious mastitis or inflammatory breast cancer, and slowly resolve over months to 1 year.[43,44]

Hematologic

Cutaneous Graft-versus-Host Disease (GVHD). GVHD encompasses all skin changes that may occur after the transplantation of an organ containing lymphoid cells and is most often seen after allogenic bone marrow transplantation.[46] GVHD is divided into acute, defined as occurring within the first 3 months after transplantation, and chronic forms. The first manifestations of chronic cutaneous GVHD occur approximately 4 months after transplantation.[46] Though the

two primary cutaneous patterns of chronic GVHD are sclerodermatous and lichenoid, the lichenoid variant includes erythematous plaques that, especially in an immunosuppressed host, may be mistaken for cellulitis.[46]

Metabolic

Gout. Acute gout produces painful joint inflammation with erythema, warmth, and swelling of overlying skin. When skin changes extend beyond the involved joint, and especially when accompanied by fever, chills, and an elevated white blood cell count, the clinical picture can resemble cellulitis.[2] Demonstration of urate crystals via joint fluid aspiration can confirm the diagnosis.[2]

Iatrogenic, Factitial, or Exogenous

Injection-site reactions. There have been several reports of cellulitis-like lesions arising at the sites of subcutaneous or intramuscular vitamin K1, or phytonadione, administered to correct coagulopathies.[47,48] The lesions represent a hypersensitivity reaction and present within 2 to 4 weeks of injection as pruritic, expanding erythematous patches, some with superimposed vesiculation or as tender, indurated, erythematous plaques.[47,48] Biopsy reveals parakeratosis, spongiosis, and a perivascular and diffuse mixed inflammatory infiltrate, mainly composed of eosinophils and histiocytes.[48]

Fixed Drug Eruption (FDE). FDE is a recurrent eruption, usually comprised of one to several round to oval, well-demarcated, erythematous and edematous plaques that occur in the same location each time the offending medication is taken. The lesions are pruritic or painful, may develop vesicles/bullae and desquamation, and typically heal with hyperpigmentation.[2,49] Though the lesions tend to favor genitalia, lips, hands and feet, they can occur anywhere.[2,49] FDE is most often associated with sulfonamides, nonsteroidal antiinflammatory drugs, barbiturates, tetracycline, carbamazepine, and at one time, phenopthaline.[50] It has been reported to occur following topotecan chemotherapy, acetaminophen, and pseudoephedrine as well.[49,51,52] When large, the lesions can resemble cellulitis.[49,51] History of recurrence, residual hyperpigmentation, skin biopsy, and rechallenge, when appropriate, can confirm the diagnosis.[2]

Vaccinations. Intramuscular vaccinations inadvertently administered subcutaneously have caused injection-site reactions that created entire extremity swelling and erythema.[53] The affected individuals did not have higher temperatures or erythrocyte sedimentation rates than those individuals with proper placement of the vaccinations.[53] Though the exact mechanism is unclear, history of vaccination helps to distinguish this condition from cellulitis, though trauma is a risk factor for cellulitis that can complicate this distinction.[53]

Contact dermatitis. Irritant contact dermatitis, resulting from the application of a noxious substance to the skin, produces well-demarcated erythematous and often pruritic skin lesions. Allergic contact dermatitis produces erythematous, swollen, often weeping or vesiculating lesions that often extend beyond the site of contact.[3] History usually elicits the causative agent, though it may be difficult to differentiate a contact dermatitis that has a superimposed cellulitis from a contact dermatitis alone. Usually, contact dermatoses do not have accompanying fever, leukocytosis, or significant pain and respond to topical corticosteroids and substance avoidance.[3]

Factitial

Silicone granulomas. Pasternack and coworkers reported a case of a woman referred for recurrent cellulitis of the lower extremities after silicone injection for cosmetic purposes years earlier.[54] Clinically, she demonstrated pain, erythema, and swelling of both lower extremities associated with fever and malaise. The lesions had been unresponsive to multiple courses of antibiotics, including linezolid. Biopsies revealed lipid granulomas consistent with silicone granulomas and the patient improved following a trial of etanercept.

Occupational

High-pressure injection injury. Although infrequent, industrial injection of foreign substances into the subcutaneous tissues has been reported multiple times in the literature.[55] Patients report an initial delayed anesthetic period followed by swelling, pain, and ischemia.[55] Many industrial greases now contain lead to assist in delineating the extent of involvement using x-rays.[55]

Toxic Exposure

Mercury. After exposure to broken thermometers, patients have developed mercury exanthems, such as circumscribed flexural pustulodermas.[56] In addition, reports exist of burning, erythematous, edematous plaques forming in the area of exposed skin.[56] These erysipelas-like mercury exanthems resolved following the use of topical corticosteroids.[56]

Infestations, Bites, and Stings

The early phases of brown recluse spiders can mimic cellulitis, presenting as erythematous, painful plaques that subsequently become cyanotic and necrotic with vesiculation and pustule formation.[57] Myiasis creates tender erythema and swelling of the affected area.[58-60] The presence of peripheral eosinophilia may aid in the diagnosis. Larval extrusion by occluding the organism's entry punctum with petrolatum jelly or antibiotic ointment confirms the diagnosis.[59,60]

Treatment of Routine Cellulitis

Treatment of routine cellulitis in immunocompetent patients can take place in the outpatient setting using a 10 to 14 day course of oral antibiotics that target *S. aureus* and *S. pyogenes*. Hospitalization with intravenous antibiotics is indicated for patients that are acutely ill, have underlying immunosuppression, present with facial cellulitis, or do not respond to oral antibiotics.[1] It is important to recognize that atypical skin infections (including cellulitis) due to community acquired methicillin-resistant *S. aureus* (CAMRSA) are rapidly increasing in prevalence. For this reason, antibiotics that cover CAMRSA (doxyxycline, trimethoprim-sulfamethoxazole, cephalosporins, macrolides, or clindamycin) are a good first-line treatment when CAMRSA is suspected and until sensitivities of bacterial cultures are finalized. Newer

agents are available for severe infections or resistant strains. Gram-negative bacteria and opportunistic organisms such as *Heliocobacter*, *Cryptococcus*, *Fusarium*, *Proteus*, and *Pseudomonas* should be considered in immunocompromised individuals.[2] Diabetics are at risk for mixed Gram-positive and Gram-negative infections, most often with *S. aureus*, *Enterococcus*, *Streptococcus, E.coli, Klebsiella, Enterobacter, Acinetobacter*, and *P. aeruginosa*.[2] When multiorganism cellulitis is suspected, broad coverage antibiotics should be instituted.[1] While response to antibiotic therapy is typically rapid, when routine cellulitis occurs in areas of compromised lymphatics, in areas of prior trauma, or in immuncompromised patients, response to therapy may be delayed.

Conclusion

The patient was diagnosed as having cellulitis in an area of chronic radiation dermatitis. She was treated with a prolonged course (6 weeks) of oral antibiotics, to which she slowly responded. This case serves to illustrate several important points about cellulitis: (1) Despite the presence of infectious cellulitis, blood cultures may not be positive for infectious organisms; (2) Routine cellulitis occurring in areas of compromised lymphatic drainage, such as chronic radiation dermatitis, is often slow to resolve even with appropriate therapy and may require an extended course of antibiotic therapy beyond the typical 10 to 14 day regimen; (3) Although cellulitis was suspected from the clinical presentation of pain, erythema, and elevated white blood cell count with neutrophilia, the differential diagnosis included carcinoma erysipeloides, which can only be confirmed histologically; (4) More than one diagnosis or more than one infectious pathogen may be present simultaneously in the immunocompromised host.

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