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A 75-year-old woman with a swollen hand and supraclavicular lymphadenopathy

The patient was an avid orchid grower

A 75-YEAR-OLD OTHERWISE HEALTHY woman presents to the outpatient clinic with painful erythema and edema of the dorsum of the left hand that has lasted for 5 days. The patient states that she initially noticed swelling and redness of the left middle finger, followed by purulent discharge at the interdigital web. This occurred while on a Caribbean cruise. She does not know of any preceding trauma. She was seen by the physician of the ship, given a tetanus shot, and started on cephalexin 500 mg four times a day. Since her symptoms did not improve, she came to our clinic for further evaluation.

Physical examination

The patient has spontaneous drainage of purulent material from the inner aspect of the left middle finger. The dorsum of her hand is edematous and erythematous with red, tender, warm, and nonpalpable longitudinal streaks over the dorsal aspect of the forearm. No axillary or epitrochlear lymph nodes are found. She has a painful, erythematous, "hot," firm, and mobile nodule measuring 3 cm by 2.5 cm on her left supraclavicular area. There is no documented history of recent trauma to the affected hand.

DIFFERENTIAL DIAGNOSIS

1 What is the most likely diagnosis?

- Cellulitis
- Acute lymphangitis
- Erysipelas
- Lymphoma

The clinical presentation in this patient is clearly related to an infectious process, but compromised lymph nodes, especially in the supraclavicular area, indicate the possibility of a malignant process with a superimposed infection. The following infections are possible, as is an underlying lymph node tumor.

Cellulitis is an acute infection of the skin and subcutaneous tissue that spreads via lymphatic and hematogenous circulation. The most frequent etiologic agents are:

- *Staphylococcus aureus*, which frequently colonizes the nasopharynx and occasionally the skin and clothing, more rarely the vagina, or exceptionally the rectum and perineal area; and
- Group A streptococci (*Streptococcus pyogenes*), which is acquired on normal skin after transmission by direct contact with infected or colonized individuals, environmental contamination, and arthropod vectors. Its transmission is influenced by geographic location, season of the year (warm and humid weather), and poor hygiene.

Most cases of cellulitis develop after a traumatic injury, such as an abrasion, cut, burn, insect bite, or surgical wound. They also may develop with underlying skin lesions, such as lymphedema, or may be caused by intravenous catheters, fungal infections, or any type of dermatitis.

Clinical manifestations include intense local inflammation, erythema, and tenderness, with poorly demarcated flat borders. Cellulitis usually involves local lymph nodes and can cause fever, chills, and malaise and



may be complicated with bacteremia. Cellulitis caused by *S aureus* spreads from a central localized infection, such as an abscess. In contrast, cellulitis from *Streptococcus* is a more rapidly spreading, diffuse process, frequently accompanied by lymphangitis and fever.

Erysipelas is a superficial type of cellulitis that spreads via the lymphatic circulation. It is almost always caused by group A streptococci, except in newborns, in whom the cause is usually group B streptococci. This infection is more common in children and older adults. Erysipelas is rarely caused by *Staphylococcus*, and infection by this agent occurs particularly in patients with chronic lymphatic dysfunction.

About 80% of the time, erysipelas is found in the lower extremities after the agent enters through skin lesions. From 5% to 20% of the time it is found on the face, usually following an upper respiratory tract infection. The lymphatic circulation can be compromised, causing obstruction of this drainage system and predisposing a patient to recurrences.

Erysipelas is characterized by an abrupt onset of fiery-red swelling of the compromised area, with intense pain. The skin lesions are superficial with a *peau d'orange* appearance; the hallmark is a well-demarcated and raised advancing border. Flaccid bullae may develop during the second or third day of illness, but extension to deeper tissues is rare. Desquamation of the involved tissue occurs 5 to 10 days into the illness.

Lymphangitis is an infection of the lymphatic channels in the skin and subcutaneous tissues caused by bacterial, mycotic, mycobacterial, or filarial microorganisms. The acute form of this disease is caused by group A streptococci. Typical manifestations include cutaneous, linear, erythematous streaks that extend from the initial site of infection toward the regional lymph nodes, as well as enlarged regional lymph nodes. The infection may recur and cause chronic lymphedema.

A distinctive form of lymphangitis, called nodular lymphangitis, also known as chronic lymphangitis or lymphocutaneous syndrome, occurs as nodular subcutaneous swellings of the involved lymphatic glands. This form of

infection develops after cutaneous inoculation of *Nocardia brasiliensis*, *Sporothrix schenckii*, *Mycobacterium marinum*, *Leishmania braziliensis*, and *Francisella tularensis*.

Lymphomas. The lymph nodes of malignant lymphomas are usually large, but not always. They are also usually firm, discrete, bilateral, mobile, and nontender, whereas nodes compromised by other metastatic cancers are usually hard and nonmovable, owing to fixation to the surrounding tissues.

In general, a firm lymph node larger than 1 cm in diameter, not infectious in origin, and persisting for more than 4 weeks outside the inguinal region should be considered for biopsy. The lymphatic drainage of the superficial tissues of the upper extremities involves the supratrochlear, axillary, and infraclavicular lymph nodes. But this drainage can sometimes cross the clavicle anteriorly and reach the supraclavicular nodes, making it possible for a lesion in the upper limb to present with a supraclavicular adenopathy.

■ INITIAL DIAGNOSIS, TREATMENT, AND OUTCOME

The patient was admitted with the diagnosis of abscess of the left middle finger, complicated with acute lymphangitis. She was started on intravenous nafcillin and underwent surgical drainage and debridement, with partial resolution of her symptoms. She received intravenous antibiotic therapy for 72 hours and was then discharged with instructions to take 500 mg of dicloxacillin by mouth four times a day. Initial culture results were negative.

Three days after being discharged, the patient returned for a follow-up visit and was readmitted because of worsening edema and erythema of her left hand. The left supraclavicular lymph node was increased in size with evidence of new erythematous tender nodules on the dorsal aspect of her wrist, forearm, and elbow. At this time, the wound cultures showed a moderate growth of gram-positive branching filamentous bacilli.

On further questioning the patient stated that she was an avid orchid grower and had been working in her greenhouse with the plants until 3 weeks before the onset of symptoms.

Consider biopsy for a firm, noninfectious lymph node > 1 cm lasting > 4 weeks

■ WHAT IS THE LIKELY ORGANISM?

2 What is the most likely organism causing the symptoms in this patient?

- Sporothrix schenckii*
- Nocardia* species
- Staphylococcus aureus*
- Mycobacterium marinum*
- Vibrio vulnificus*

All of the organisms listed are possible causes of this patient's symptoms.

Sporothrix schenckii is a fungus that causes infections after inoculation into subcutaneous tissue via minor trauma. Nursery workers, florists, and gardeners acquire the illness from roses, sphagnum moss, and other plants. The initial lesion, at the site of the inoculation, is usually a painless papule, pustule, or nodule that ulcerates, developing raised erythematous borders. This is followed by the classic lymphangitic spread of nodules in a linear fashion. The nodules are erythematous, painless, and of varying size, localized along the lymphatic channels, and classically with no involvement of lymph nodes. The lesions may become chronic, waxing and waning for months or years. Identifying sporotrichosis in the laboratory is often difficult since the fungus usually cannot be seen in the specimens of the lesions. In inoculated laboratory animals or rarely in human tissue specimens, *S schenckii* appears as round or cigar-shaped budding yeast cells. In culture, the hyphal form is usually identified.

Nocardia is an actinomycete, identified by Gram stain in wound drainage or tissue specimens as filamentous branching gram-positive aerobic rods. *N asteroides* is the major human pathogen, along with *N brasiliensis*, and *N otitidis-caviarum*. It is a common inhabitant of soil (especially in organic matter), house dust, beach sand, and swimming pools. No evidence exists of person-to-person transmission. It can be inhaled and may cause pneumonia and sometimes even hematogenous dissemination, particularly to the central nervous system and skeletal soft-tissue structures, in patients with impaired cell-mediated immunity. It is also a cause of cellulitis, lymphocutaneous syndrome, and actinomycetoma after direct skin inoculation.

Staphylococcus aureus is the most common cause of skin and soft tissue infections, including cellulitis, suppurative lymphadenitis, infections originating in the hair follicles, bullous and nonbullous impetigo, and infrequently, erysipelas and acute lymphangitis. It is part of the endogenous flora, harbored in the nares or other sites of colonization.

In *S aureus* infections, the compromised lymph nodes are usually tender, swollen, and at least 3 cm in diameter. Fever is commonly present, and the overlying skin is usually painful, erythematous, warm, and edematous. If lymphangitis develops, erythematous streaks can be seen.

Mycobacterium marinum is an atypical mycobacterium found in swimming pools and fish tanks. It can cause a cutaneous infection, usually a small violet papule on the hand or arm. This may progress to a shallow crusty ulceration with scar formation, the so-called "swimming pool" or "fish tank" granuloma, or can produce cellulitis on skin surfaces exposed to the contaminated water. Most infections occur 2 to 3 weeks after contact with contaminated water from one of these sources. The lesion is usually solitary, but occasionally the patient may develop secondary ascending lesions as in sporotrichosis. The diagnosis is made by culture and histologic examination of biopsy material, along with a compatible history of exposure.

Vibrio vulnificus causes two distinct syndromes. One is a primary wound infection following contact of a fresh wound with contaminated seawater. This disease begins with swelling, erythema, and in many cases, intense pain around the initial lesion. Rapidly spreading cellulitis follows, with vesicular, bullous, or necrotic lesions developing in some instances. Metastatic lesions rarely occur.

The other syndrome linked to *V vulnificus* is primary sepsis after ingestion of contaminated seafood in patients with underlying liver disease or immunosuppression. Secondary cutaneous lesions develop in three fourths of cases, typically involving the extremities. A common sequence is the evolution of erythematous patches followed by ecchymoses, vesicles, and bullae. Necrosis and sloughing may occur.

***Nocardia* is commonly found in soil**



■ COMMON SYMPTOMS OF SYSTEMIC NOCARDIOSIS

The final report of this patient's wound culture was positive for *N brasiliensis*. We suspect that the patient acquired the infection while she was working in her orchid garden.

3 What are the more common presentations of systemic nocardiosis?

- Pulmonary involvement
- Central nervous system (CNS) involvement
- Actinomycetoma
- All of the above

Impaired cell-mediated immunity is a well-established risk factor for nocardiosis; therefore, infections with this pathogen should be considered opportunistic and sometimes life-threatening if they progress to disseminated disease in organ transplant recipients or in patients with lymphoreticular neoplasias. Other risk factors include chronic obstructive pulmonary disease, pulmonary alveolar proteinosis, HIV infection, alcoholism, diabetes, and long-term use of steroids.

Pulmonary involvement is the most common presentation of nocardial infections. The presentation can vary but is usually suppurative. Patients may develop pneumonia, lung abscesses, empyema, and cavitary lesions. Radiologic findings can vary from nodules to unspecific reticulonodular infiltrates, cavitary lesions, and pleural effusions. Nocardiosis should always be considered in the differential diagnosis of indolent pulmonary disease in immunocompromised patients.

CNS involvement is a slow, progressive process. Symptoms usually develop over months to years and can cause a broad range of neurologic deficits, including psychiatric disorders that reflect focal neurologic involvement by granulomas or abscesses. CNS nocardiosis can be easily mistaken for neoplasia because of the slow development of neurologic symptoms, silent invasion, and paucity of clinical and laboratory signs of bacterial infection. Brain biopsy should be considered early in an immunocompromised patient since the course of the disease tends to be more aggressive. The mortality rate in patients with

nocardial brain abscesses can be as high as 40% to 50%.

Actinomycetoma, along with cellulitis and lymphocutaneous syndrome, are forms of subacute or chronic suppurative inflammation in the subcutaneous tissues induced by *Nocardia* when inoculated into the skin. *Nocardia* produces progressive necrosis, fibrosis, and sinus tract formation with destruction of adjacent structures. Actinomycetoma is the typical name for these lesions, which appear days or months after the organism penetrates the skin, most frequently in the distal portion of the limbs.

Actinomycetoma is characterized clinically by a progressive painless subcutaneous nodule, with sinus tracts that drain purulent material that contains granules. The differential diagnosis should include eumycetoma caused by *Eumycota* fungal infections, and actinomycetoma caused by other actinomycetes. Cutaneous nocardiosis and mycetoma can occur in immunocompetent patients and can resolve spontaneously. When it spreads through the lymphatic channels, from the primary lesion toward the regional lymph nodes, *Nocardia* causes nodular lymphangitis that has a subacute or chronic course and should be differentiated from lesions caused by *S schenckii*, *M marinum*, *Leishmania braziliensis*, and *Francisella tularensis*. Some of the skin lesions of nocardiosis are self-limited and may be disregarded or treated as staphylococcal infections. Inoculation into the eye can also happen after corneal trauma, and can produce keratitis.

■ TREATMENT OF NOCARDIOSIS

Treatment of *Nocardia* consists of antibiotic therapy and surgical drainage and excision of involved tissue. The selection of antibiotics depends on the site of the infection, the severity of the disease, and the general condition of the patient. Sulfonamides are the mainstay of therapy for infections caused by *N brasiliensis* and *N asteroides* complex. Trimethoprim-sulfamethoxazole is the most commonly used form of sulfonamides, with dose adjustments for renal function and severity of disease.

Amikacin and imipenem are two alternative antibiotic agents for severe or disseminated infections. They can also be used in combi-

Impaired immunity is a risk factor for nocardiosis



nation with trimethoprim-sulfamethoxazole. Many isolates of *N brasiliensis* are resistant to imipenem, however.

The length of therapy is controversial. For patients with cutaneous nocardiosis, 3 to 6 months of therapy is acceptable. Prolonged therapy is required for patients with mycetoma. Patients with pleuropulmonary disease should be treated at least for 6 months and patients with CNS involvement should complete 12 months of therapy.

Because this patient had severe symptoms, she was initially treated for 2 weeks with intravenous amikacin and imipenem, followed by oral trimethoprim-sulfamethoxazole. Her lesions began to improve after a few days of therapy. She was discharged home and instructed to complete 6 months of therapy with oral trimethoprim-sulfamethoxazole.

■ ALTERNATIVE TREATMENTS FOR PATIENTS ALLERGIC TO SULFA DRUGS

4 In patients with nocardiosis who are allergic to sulfa drugs, what alternative antibiotics can be used?


- Amikacin
- Imipenem
- Amoxicillin-clavulanate
- All of the above

All of these agents can be used to treat patients allergic to sulfa drugs.

Amikacin and imipenem, as noted above, are two alternative antibiotic agents for severe or disseminated infections, and are often used in combination with trimethoprim-sul-

famethoxazole. However, they can also be used alone in patients allergic to sulfa drugs.

Amoxicillin-clavulanate or **minocycline** can be used generally in combination with amikacin for CNS infections in patients who require oral medication other than trimethoprim-sulfamethoxazole. **Ceftriaxone**, **cefotaxime**, and **cefuroxime** are used for CNS infections because of their excellent cerebrospinal fluid penetration and low toxicity.

Doxycycline, **erythromycin**, **clarithromycin**, **ampicillin**, **dapsone**, and **fluoroquinolones** may be used according to in vitro susceptibility. Isolates of *N otitidis-caviarum* are usually resistant to sulfamethoxazole. 

■ SUGGESTED READING

- Beaman L, Beaman BL.** Nocardia species: host-parasite relationships. *Clin Microbiol Rev* 1994; 7:213-264.
- Clark NM, Braun DK, Pasternak A, Chenowith CF.** Primary cutaneous *Nocardia otitidis caviarum* infection: case report and review. *Clin Infect Dis* 1995; 20:1266-1270.
- Goldman L, Bennett JC.** Cecil Textbook of Medicine, 21st ed. Philadelphia: W.B. Saunders, 2000:1885-1887.
- Henry PH, Longo DL.** Enlargement of lymph nodes and spleen. In Fauci AS, Braunwald E, Issenbacher KJ, et al, editors. *Harrison's Principles of Internal Medicine*, 14th ed. New York: McGraw-Hill, 1998:345-347.
- Khardori N, Shawar R, Gupta R.** Antimicrobial susceptibilities of *Nocardia sp.* *Antimicrob Agents Chemother* 1993; 37:883-884.
- Kostman JR, DiNubile MJ.** Nodular lymphangitis. *Ann Intern Med* 1993; 118:883-888.
- Lerner PI.** Nocardiosis. *Clin Infect Dis* 1996; 22:891-905.
- Mandell GL, Bennett JE, Dolin R.** *Nocardia* species. In *Principles and Practice of Infectious Diseases*, 5th ed. Philadelphia: Churchill-Livingstone, 2000:2637-2645.
- Williams PL, Warwick R, Dyson M, et al.** *Angiology*. In *Gray's Anatomy*, 37th ed. New York: Churchill-Livingstone, 1989:845-847.

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Sulfonamides are a common treatment for nocardiosis

CORRECTIONS

The answer key to the August 2000 CME Credit Test contained an error. The answer to question 8 (Transmyocardial revascularization entails creation of small channels in the myocardium using:) should have been B—a laser.

The answer key to the September 2000 CME Credit Test also contained an error. The answer to question 10 (True or false? Clinical symptoms of diabetic gastropathy are well correlated with the rate of gastric emptying) should have been B—false.

On page 737 in the article by Mario J Garcia, "Diastolic dysfunction and heart failure: Causes and treatment options" in the October issue, the word "precipitate" was omitted from the following sentence: However, aggressive diuresis can significantly decrease cardiac output and precipitate prerenal azotemia due to the steep pressure volume relationship characteristic of the "stiff" left ventricle (**FIGURE 3**).

We apologize for these errors and thank all the readers who pointed them out.