Nodular Lymphangitis: A Distinctive but Often Unrecognized Syndrome

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■ *Purpose:* To describe nodular lymphangitis by reviewing the clinical and epidemiologic features of this disease with an emphasis on distinguishing specific etiologic agents.

■ *Data Sources:* English-language articles were identified through a MEDLINE search (1966 to September 1992) using sporotrichosis, lymphangitis, and sporotrichoid as key words; additional references were selected from the bibliographies of identified articles. In addition, three new patients with nodular lymphangitis are described.

■ *Study Selection:* One hundred fifty articles were reviewed to determine details of the etiologic agents and clinical signs and symptoms of patients with nodular lymphangitis.

■ *Data Synthesis:* Nodular lymphangitis develops most commonly after cutaneous inoculation with *Sporothrix schenckii*, *Nocardia brasiliensis*, *Mycobacterium marinum*, *Leishmania braziliensis*, and *Francisella tularensis*. The setting in which infection is acquired is useful in differentiating among the various organisms causing infection. Sporotrichosis and leishmaniasis can have longer incubation periods than do the other common causes of nodular lymphangitis. A painful ulcer at the site of the initial lesion suggests tularemia; frankly purulent drainage often accompanies infections with *Francisella* and *Nocardia* species. Ulcerated or suppurating lymphangitic nodules occur commonly with *Nocardia* infections. Patients with nodular lymphangitis who fail to respond to empiric treatment for sporotrichosis should be evaluated for other organisms with appropriate biopsies and cultures.

■ *Conclusions:* Nodular lymphangitis has distinctive clinical signs and symptoms, most commonly due to infection with a limited number of organisms. A detailed history, accompanied by information obtained from skin biopsy specimens using appropriate stains and cultures, should allow specific, effective therapy for most of these infections.

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Acute lymphangitis, recognizable as linear erythematous streaks extending from the primary lesion toward the regional lymph nodes, often accompanies group A streptococcal infections. In southeast Asia, recurrent episodes of lymphangitis involving the lower extremities are important early findings in Brugian filariasis. Lymphangitis in association with recrudescent inflammation at the original wound site differentiates rat-bite fever due to *Spirillum minor* from the similar illness caused by *Streptobacillus moniliformis*.

A distinctive form of lymphangitis occurs as nodular subcutaneous swellings along the involved lymphatic glands. Lymphatic involvement is suggested by the clinical appearance, but only rarely has there been pathologic documentation of the site of inflammation (1). The characteristic manifestations of "nodular lymphangitis," often subsumed under such imprecise descriptions as chronic lymphangitis or the lymphocutaneous syndrome, should suggest infection with a circumscribed group of microorganisms. After describing three patients we have recently encountered, we review the causes of "nodular lymphangitis" (Table 1), emphasizing the use of epidemiologic and clinical features to distinguish the specific entities (Table 2).

Case Reports

Patient 1

A elderly man complained of purulent drainage from a minor abrasion of his hand that occurred when he fell in a wet city street approximately 1 month earlier. He was afebrile, and there were no systemic symptoms or signs. Tender nodular swellings were present along the involved arm (Figure 1, *left*). No lymphadenitis was noted. *Nocardia brasiliensis* was cultured from the pus.

Patient 2

A young woman complained of pain and swelling of her right ankle, which she had scraped a few weeks earlier while walking on a rural path in Japan. After the wound had healed, she developed swelling, erythema, and pain around the ankle after removal of the eschar. She had low-grade fever, accompanied by painful erythematous nodules extending up the right leg, and she had tender nonsuppurative lymph nodes in the right groin. *Nocardia brasiliensis* was cultured from a skin biopsy specimen of the right lower extremity cellulitis.

Patient 3

A middle-aged woman cut her index finger while working with a paring knife. Several weeks later, she

Table 1. Organisms That Can Cause Nodular Lymphangitis

Common causes
Sporothrix schenckii
Mycobacterium marinum
Nocardia brasiliensis
Leishmania braziliensis
Francisella tularensis
Unusual causes
Nocardia asteroides
Mycobacterium chelonae
Leishmania major
Rare causes
Mycobacterium kansasii
Blastomyces dermatitidis
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Streptococcus pyogenes
Staphylococcus aureus
Pseudomonas pseudomallei
Bacillus anthracis
Cowpox

developed purulent drainage from the nonhealing wound. She had a low-grade fever and nontender nodules extending up her forearm (*see* Figure 1, *right*). There was no adenopathy. A culture of the primary lesion yielded *Nocardia asteroides*.

Causes of Infection

The frequency with which an organism causes nodular lymphangitis depends on the frequency of cutaneous infections with that organism and on the likelihood that nodular lymphangitis will develop after a skin infection. In the following discussion, the distribution of causative organisms is assumed to parallel the frequency of reported patients with nodular lymphangitis. However, this is likely to vary by geographic region and mode of acquisition.

Nocardia Species

Nocardia species (predominantly *N. asteroides*) cause subacute disseminated pyogenic infection, often involving the lung, brain, and subcutaneous tissues in patients with impaired cell-mediated immunity (2). Immunocompetent patients can develop primary cutaneous nocardiosis, generally manifested as a single tender abscess or ulcerated papule a few days to 6 weeks after incurring a minor wound contaminated with soil (3-9).

Patients infected with *N. brasiliensis* (or less commonly *N. asteroides*) may have nodular lymphangitis, sometimes associated with regional adenopathy and mild systemic symptoms (3-20). The initial wound may drain frank pus or have already healed except for a dry scab and surrounding erythema (4, 8, 10, 15).

In the largest review of *N. brasiliensis* infections in the United States, 11 of 41 patients with skin or soft tissue infections had an associated nodular lymphangitis (21). The lymphangitic nodules often ulcerate or suppurate (4, 11, 15, 16, 19) (*see* Figure 1).

Nocardia can be identified by Gram stain in wound drainage or tissue specimens as delicate branching gram-positive rods; most species are acid fast when stained with a modified Ziehl-Neilson stain. The diagnosis can be confirmed by isolation of the organism. Short courses of therapy with trimethoprim-sulfamethoxasole, sulfadiazine, or minocycline probably hasten resolution (3, 17, 18).

Sporothrix schenckii Infections

Sporothrix schenckii is the most commonly recognized cause of nodular lymphangitis encountered in the United States. This dimorphic fungus is found in soil and plant debris such as sphagnum moss (22). Sporotrichosis is most often seen in Oklahoma and along the Missouri–Mississippi river valleys (23). The disease is also common in Mexico and elsewhere in Central America as well as in the Far East (24).

Inoculation sporotrichosis characteristically manifests

Table 2. Nodular Lymphangitis: Major Causes and Differentiating Features

Etiologic Organism	Geographic Distribution	Habitat	Incubation Period (*wks*)	Primary Lesion	Lymphadenitis	Systemic Symptoms
Sporothrix schenckii	Worldwide in pockets	Soil	1 to 12	Painless ulcer	Occasionally	None
Leishmania species (usually *L. braziliensis*)	Tropics and subtropics	Small rodents and dogs (sandfly vector)	2 to 24	Painless well-demarcated ulcer (unless superinfected)	Occasionally	None
Nocardia species (usually *N. brasiliensis*)	Worldwide	Soil	< 1 to 6	Mildly to moderately tender ulcer or abscess (sometimes healed)	Commonly	Mild
Mycobacterium marinum	Worldwide	Water	Usually 2 to 3	Mildly tender papule (with suppuration)	Occasionally	None
Rapidly growing Mycobacteria (usually *M. chelonae*)	Worldwide	Soil and water	?	Tender nodule with cellulitis	Occasionally	None
Francisella tularensis	Northern hemisphere	Wild mammals and ticks	< 1	Painful ulcer	Almost always	Moderate to severe

Figure 1. Two patients with nodular lymphangitis. Nodular lymphangitis caused by *Nocardia* species involving the upper extremities in two immunocompetent patients from the Philadelphia area. Left. *N. brasiliensis.* Right. *N. asteroides.*

as a lymphocutaneous infection 1 week to 3 months after a traumatic injury incurred while gardening (22-24). A nodule or shallow ulcer typically forms at the inoculation site, frequently accompanied by more proximal erythematous nodules along the involved extremity. Local discomfort is usually mild. Prominent lymphadenitis and systemic complaints, such as fever and chills, are unusual.

The diagnosis is made by recognition of the clinical syndrome in the appropriate epidemiologic context and by presence of the yeast in tissue using immunofluorescence (3), or by isolation of the organism in culture, or both. Potassium iodide, itraconazole, or local heat are usually effective therapies (22, 25).

Leishmania Species

New world cutaneous leishmaniasis is endemic in rural areas of Central and South America (26-30). Cutaneous leishmaniasis of the old world occurs as a rural and urban disease in the Middle East and in large parts of tropical and subtropical Africa and Asia (1, 31, 32). The parasites are transmitted by the bite of ground-dwelling sand flies. Between 2 to 24 weeks later, a small nodule appears at the inoculation site that usually evolves into a well-demarcated ulcer. Satellite lesions can form around the original lesion. There is often an associated seropurulent discharge. Local pain is typically mild, unless bacterial superinfection of the ulcer occurs. Although regional lymphadenopathy occasionally develops, systemic symptoms rarely occur.

"Sporotrichoid" lymphangitis frequently accompanies cutaneous leishmaniasis of the new world caused by members of the *Leishmania braziliensis* complex, especially when *L. b. panamensis* or *L. b. guyanensis* is the causative subspecies (27, 29, 30). Nodular lymphangitis develops less commonly in patients with old world cutaneous leishmaniasis due to *Leishmania major* (1, 31, 32). Infections with the *Leishmania mexicana* complex, *Leishmania tropica*, and *Leishmania aethiopica* rarely cause lymphangitis.

Leishmania amastigotes can be identified in material aspirated from the border or scraped from the base of the ulcer. The natural history and response to therapy are species specific (27-30, 33, 34). Cutaneous leishmaniasis will resolve spontaneously in many patients. Recently, allopurinol has been used successfully as monotherapy for American cutaneous leishmaniasis (35).

Mycobacteria Species

Mycobacterium marinum

Mycobacterium marinum is a photochromogenic acid-fast organism associated with fresh and salt water (36-40). Human infection usually occurs after injuries in aquariums, swimming pools, or other bodies of water, or injuries related to fish spines. After a variable incubation period, often 2 to 3 weeks, a mildly tender papule forms on the injured extremity that slowly enlarges and suppurates. Nodular lesions may develop along the draining lymphatic glands, but regional lymphadenitis and systemic complaints are uncommon (36-47).

The diagnosis of *M. marinum* is usually made by identifying the organism in infected tissue or pus. Cultures should be incubated at 32 °C (37-39). Debridement is frequently required. Rifampin, ethambutol, trimethoprim-sulfamethoxasole, minocycline, or all of these agents have been used successfully to treat this infection; therapy is often continued for 4 to 6 weeks after healing of the lesions (42, 44, 46).

Other Mycobacteria

Mycobacterium fortuitum and *Mycobacterium chelonae* are the major human pathogens among the rapidly growing mycobacteria (36, 48). These organisms have been recovered from soil and water; human disease usually occurs after accidental trauma or surgical contamination. In contrast to patients who develop disseminated disease, those patients with localized infection, with or without nodular lymphangitis, are usually immunocompetent. Although cutaneous disease due to rapidly growing mycobacteria is well described, only a few patients with nodular lymphangitis have been infected with *M. chelonae* (49-51).

The isolation of rapidly growing mycobacteria from the wound can be accomplished in 5 to 7 days. Treatment entails surgical debridement with combinations of

antibiotics optimally determined by susceptibility testing of the particular isolates (48, 52-54).

Mycobacterium kansasii is a photochromogenic acid-fast organism that has a world-wide distribution (36, 55). The natural habitat of the organism is unknown, but it is an uncommon environmental contaminant. The rare instances of nodular lymphangitis due to *M. kansasii* have been characterized by indolent, verrucous growths at the site of inoculation and subcutaneous nodules along the involved lymphatics without regional lymphadenopathy (55, 56). *Mycobacterium kansasii* can be cultured from biopsy specimens of the primary lesions. Therapy should include antibiotic combinations dictated by susceptibility testing (57).

Francisella tularensis Infections

Francisella tularensis is a gram-negative coccobacillus distributed throughout the United States; infections have occurred most commonly in Texas, Oklahoma, Arkansas, Tennessee, and Missouri (58-60). Most patients acquire the disease from contact with infected mammals (for example, rabbits) or from bites of infected arthropods.

The ulceroglandular form of tularemia occasionally occurs as nodular lymphangitis (59). A tender ulcer usually develops at the inoculation site within 3 to 5 days, although the incubation period sometimes may be as long as 2 weeks. Accompanying findings typically include severe constitutional symptoms and painful lymphadenopathy. Diagnosis is made by serologic confirmation in the appropriate epidemiologic setting. Streptomycin is the drug of choice for tularemia; relapses are more frequent after treatment with tetracyclines (60).

Other Causes

Nodular lymphangitis has been reported (61-64) as developing after infections with a diverse group of organisms. These have included "routine" pyogenic bacteria (like *Staphylococcus aureus* and *Streptococcus pyogenes*), *Pseudomonas pseudomallei*, and *Bacillus anthracis*. Various fungi other than *Sporothrix*, including *Coccidioides immitis* (65-68), *Blastomyces dermatitidis* (69-71), *Histoplasma capsulatum* (72-74), and *Cryptococcus neoformans* (75, 76), have infrequently been reported to cause nodular lymphangitis. These infections have almost always occurred in pathologists or laboratory workers after inoculation accidents. A single report exists of nodular lymphangitis due to vaccinia (cowpox) virus (77).

Differential Diagnosis

In differentiating the causes of nodular lymphangitis, the epidemiologic setting in which infection develops is an important factor. *Leishmania braziliensis* is unlikely to be acquired in the United States outside of Texas (27). Tularemia is confined to the northern hemisphere (59). Lymphocutaneous disease contracted in southeast Asia could be due to melioidosis (62). A history of a traumatic wound, even when minor, contaminated with soil should suggest sporotrichosis, nocardiosis, or rapidly growing mycobacterial infection. However, infections after injuries incurred while gardening are not invariably caused by *Sporothrix* (4-6, 8, 10, 39, 55). A wound in contact with water makes *M. marinum* a more likely pathogen (37). Hunting or tick exposure implicates *F. tularensis* (59, 60). Infections with *Bacillus anthracis* occur after agricultural or industrial exposure to animals or their products in areas of the world where anthrax is enzootic (64). Pathologists and microbiologists working with certain fungi can develop skin infections after laboratory accidents (66, 67, 70, 73, 74).

As outlined in Table 1, the likelihood of developing nodular lymphangitis after a skin infection depends on the specific causative organism. Cutaneous infections with *Sporothrix schenckii*, *L. b. panamensis* and *guyanensis*, *N. brasiliensis*, *M. marinum,* and *F. tularensis* are the most probable infections to be complicated by nodular lymphangitis. These syndromes usually, but not invariably, occur in immunocompetent hosts and remain confined to lymphocutaneous structures (2, 16, 47, 78).

An estimation of the incubation period can provide additional help in predicting the infecting agent. Infections due to *F. tularensis*, *Streptococcus pyogenes*, *Staphylococcus aureus,* and *P. pseudomallei* have the shortest incubation periods, typically less than 1 week. *Nocardia* infections may also have a relatively brief incubation period (frequently less than 2 weeks) (4-6). The time between inoculation and development of disease often substantially exceeds 2 weeks for infections caused by *Sporothrix* and *Mycobacteria* species.

The initial cutaneous lesions seen in sporotrichosis, leishmaniasis, nocardiosis, and tularemia are typically ulcerated papules. In mycobacterial disease, the primary lesions tend to be more nodular. Only *F. tularensis* commonly causes painful ulcers, accounting for their apt description as "chancriform." Tender lesions can also accompany infections with pyogenic bacteria. Nocardial lesions often exude frank pus, whereas mycobacterial lesions usually have thinner seropurulent drainage (8, 15). Multiple primary lesions may occur with any of these organisms. The lymphangitic nodules themselves can sometimes ulcerate and suppurate, especially in *Nocardia* infections (8, 10-12, 15, 16, 19, 20, 23, 37, 39, 55) (*see* Figure 1, *left*).

Although regional adenopathy commonly develops in patients infected by *N. brasiliensis*, it is less frequent in sporotrichosis and disease due to *M. marinum*. *Francisella tularensis* routinely involves the regional lymph nodes, as implied by the designation "ulceroglandular tularemia"; the associated lymphadenitis is painful. Tender lymphadenitis is also commonly found in infections with *Streptococcus pyogenes*, *Staphylococcus aureus*, and *P. pseudomallei*. Severe systemic complaints are uncommon with most causes of nodular lymphangitis. Exceptions include tularemia and melioidosis that frequently have distressing constitutional symptoms including fever, chills, myalgias, and headache (59-61). Systemic complaints often accompany streptococcal and staphylococcal infections.

Lack of response to therapy can be used as a discriminating diagnostic tool. Patients who have nodular lymphangitis due to pyogenic bacteria (a rare event)

often respond promptly to the standard antibiotic regimens used to treat cellulitis. Many patients who have nodular lymphangitis are treated as though they have sporotrichosis and they do not receive a definitive diagnosis. In this setting, failure of the patient to respond should prompt consideration of other causes, prioritized according to the clinical context. However, apparent responses can be misleading because spontaneous recovery is not uncommon in many of these infections. Appropriate smears and cultures of biopsy specimens can establish the diagnosis in most patients.

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"Great principles", such as the "uniformity of nature", the "law of universal causation", and so on, are attempts to bolster up our belief that what has often happened before will happen again, which is no better founded than the horse's belief that you will take the turning you usually take. . . . The final conclusion is that we know so much, and still more astonishing that so little knowledge can give us so much power.

Bertrand Russell
ABC of Relativity
Unwin Paperbacks, London, 1985, pp. 151, 155

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