FEATURE ARTICLE

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Leprosy and Lack of Awareness in U.S. Clinicians

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ABSTRACT: Hansen's disease, synonymously and commonly referred to as leprosy, is an important consideration when treating any chronic skin disorder and rheumatologic disorder. Personal clinical experience and a review of the literature highlight a lack of awareness for this disease by U.S. clinicians. In this country, accurate diagnosis is delayed. One cannot ensure swift and proper treatment without timely, accurate diagnosis. Unfortunately, severe debilitating nerve and tissue damage can occur within months.

The authors draw upon recent personal and clinical experiences diagnosing and treating cases of the disease during a current resurgence in Florida. The authors aim to encourage readers to increase awareness for this ancient disease. In doing so, its relevance today and essential points in diagnosis and treatment are emphasized. This article is a compilation of our recent clinical experiences, in consultation with one of the world's leading authorities in the diagnosis and treatment of the disease and its complications: The National Hansen's Disease Program within the U.S. Department of Health and Human Services, Health Resources and Services Administration, Baton Rouge, Louisiana.

Key words: Accurate Diagnosis, Hansen's Disease, Lack Clinician Awareness, Leprosy, Rheumatological, Skin Disorder

Hansen's disease, synonymously and commonly referred to as leprosy, is an important consideration when treating any chronic skin disorder or rheumatologic disorder. This important fact struck personal and professional notes when Volusia County, in northeastern Florida, our home county, reported three new cases in 5 months. Our community drew local and national attention with television investigative reporting. For example, Good Morning America reported a story on February 27, 2015 (Mohney, 2015). The authors of the article below draw from recent personal and clinical dermatology experiences diagnosing and treating two of these three cases, whereas one case includes the diagnosis and treatment of a consequence of the disease involving a complication: Hansen's disease type 1 reversal (T1R) reaction versus type 2 reaction, erythema nodosum leprosum (ENL).

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HISTORICAL PERSPECTIVE

Our country's National Hansen's Disease Program, formerly located in Carville, Louisiana, has been caring and curing since 1894, according to a recent Hansen's Museum Virtual Tour available at www.hrsa.gov/hansensdisease/museum. In 1992, the National Park Service placed Carville Historic District on the National Register of Historic Places.

Leprosy derives from the Latin word, "lepra," meaning scaly. This disease is a bacterial infection. The synonym, Hansen's disease, credits Gerhard Armauen Hanse, a physician, for his 1873 discovery in Norway, the bacterial bacillus pathogen *Mycobacterium leprae* (World Health Organization, 2015). It is a fragile pathogen that multiplies very slowly. For example, an incubation range is reportedly 9 months to 20 years. Symptom appearance may follow this time frame. It is not highly contagious (Hope for Hansens, 2012). Indeed, 95% of humans are naturally immune. For unknown reasons, a few people lack this immunity and may become infected when exposed to untreated infected human or animal hosts (Texas Department of State Health Services, 2015).

Disease Prevalence

This disease is rare in this country. Furthermore, T1R reaction and the ENR reaction are even lesser known encountered clinical experiences in the United States. The disease is a reportable one federally as well as within most states. In fact, the Centers for Disease Control and

Prevention (CDC) reported an annual incidence of newly diagnosed cases of this disease in the United States to be 0.52 cases per million. Furthermore and according to the CDC, regions of the United States are endemic (Nolen et al., 2014). For the past few years, our nation's Gulf Coast region reported 100–150 cases per year according to Nolen et al. (2014). The most recent national data available and reported on March 2015 evidenced that the following states accounted for nearly 70% of reported cases: Texas, 36; Hawaii, 35; New York, 34; California, 32; Florida, 30; Louisiana, 21; and Massachusetts, 15 (D. Scollard, MD, PhD, Director, The National Hansen's Disease Program, Baton Rouge, LA, personal communication, April 26, 2015). According to Florida Volusia county health officials, previously, the state typically reported 8–10 cases annually. Furthermore, The National Hansen's Disease Program data and statistics (United States) indicated that, of these new cases, 68% were male whereas the ages of all individuals ranged in years from 11 to 92. A genetic study was completed at the National Hansen's Disease Program and evidenced that armadillos may be a source of the infection in the southeastern United States. Truman et al. (2011) wrote that infected armadillos have been reported in Alabama, Arkansas, Louisiana, Mississippi, Texas, and Mexico. For example, the species (nine-banded armadillo, *Dasypus novemcinctus*) was introduced to Florida by armadillo spread or migration from Texas as well as armadillos released into the wild along the Atlantic coast (living exhibits at the Museum of Science and Industry, Tampa, FL, personal communication, May 29, 2015). Transmission of the disease from an infected armadillo to a human can be by means of a fomite, such as soil (Truman et al., 2011). For example, consider a construction worker reporting to work day in and day out handling items with bare hands at a work site frequented, scoured, and foraged by the nocturnal creatures.

The National Hansen's Disease Program is the epicentrum of care, research, and information for the disease in this country. Human to human, the disease is transmitted via droplets from noses and mouths with close and frequent contacts with untreated infected people. Fortuitously, people become noninfectious quickly and often after initiating only a few doses of the appropriate multiple drug therapy. Hence, there is no need to isolate patients from family, friends, and coworkers. In fact, once accurately diagnosed and correct treatment ensues, patients are able to continue with their usual lifestyle. Cure, however, requires long-term treatment. Compliance may be an issue because treatment is often months to years and potentially a lifetime.

LACK OF AWARENESS

Unfortunately, in this country, accurate diagnosis is delayed because of lack of clinician awareness of the disease. According to the CDC, most cases in this country had a delay approaching 3 years (number of years of onset symptoms to Hansen's disease accurate diagnosis), with a median delay of about a year and a mean of roughly 2 years for both U.S.- and foreign-born patients. It is important to note that, without proper treatment, severe nerve and tissue damage can occur within months to years. Roughly 25% of reported cases, including U.S. and foreign born, had reported symptoms lasting more than 3 years before an accurate diagnosis was made.

The diagnosis, Hansen's disease, is an important consideration in any chronic skin disorder and rheumatologic disorder. Cutaneously and commonly, early presenting symptoms include a pale or reddish skin patch with diminished sensation. In addition to diminished sensation or anesthetic cutaneous lesion(s), mucous membrane lesions often evidence thickened peripheral nerves histopathologically (Abraham et al., 1998; Kline, Powers, & Defazio, 2015). "Leprosy often presents as a rheumatologic disorder including lupus erythematous, rheumatoid arthritis, or anticardiolipin syndrome" (Rendini & Levis, 2015, p. 448). Furthermore, clinician awareness must heighten and remain sustained in this unprecedented era of biological therapies.

Although recognized in ancient civilizations of China, Egypt, and India, a first known written mention of the disease dates back to 600 B.C. There was no cure. Ironically, armadillos acquired the disease from humans after colonization of the New World (Truman et al., 2011). A breakthrough in treatment occurred with the development of dapsone in the 1940s, but by the 1960s, resistance was evident. Rifampicin and clofazimine were discovered shortly thereafter providing two additional components to a multiple-drug therapy treatment plan. By 1981, a World Health study group recommended that these three drugs serve as the standard multiple-drug therapy treatment as they kill the pathogen and cure the patient.

Resources to Increase Clinician Awareness

A free online course offering 1 contact hour of continuing education is available and titled, "Awareness of Hansen's Disease in the U.S.: Basic diagnosis, treatment, and management of complications" (U.S. HHS HRSA, 2015b). It was designed and presented by the National Hansen's Disease Program to increase awareness. The authors of the course cite additional intentions to:

- provide all healthcare providers with knowledge needed to diagnose and treat the disease;
- introduce methods used to prevent disabilities caused by the disease; and
- aid in the diagnosis and management, including complications.

CASE PRESENTATION: ACCURATE DIAGNOSIS, HANSEN'S DISEASE

On September 2013, a 58-year-old Caucasian male established patient, accompanied by his wife, presented to our

office for an episodic visit with a chief complaint of red skin lesions on the right thigh with a 2-month duration and denial of self-treatment. Past medical history was significant with a history of never smoking, basal cell carcinoma, atopy, and hypercholesterolemia. Current medications included Flonase nasal spray, levothyroxine, Lipitor, and Tricor. Clinical examination was consistent with a cutaneous hypersensitivity reaction as evidenced by erythematous macules coalescing into patches and distributed on the bilateral thighs, with right greater than left. Two lesions were noted to exhibit central clearing without scaling. A potassium hydroxide (KOH) preparation showed no hyphae. A plan of care was prescribed: triamcinolone 0.1% topical cream twice a day for 2 weeks. Patient education included instructions for the patient to return to the office if the plan of care was not effective. In addition, the patient had an annual skin cancer screening, including a complete skin examination, scheduled the following month.

Indeed, 1 month later, the patient returned stating that he followed the prescribed plan of care but the lesions persist, "no better, just there," denying symptoms. His exposure to armadillos was discovered. He reported killing and burying them in his yard because of his growing frustration with their destruction of his yard. The clinical impression was basically unchanged, and the impression evolved into an unspecified rash, with erythematous plaques predominating on the right thigh. A 4-mm punch biopsy (hematoxylin and eosin stain) was collected at this office visit and, ultimately, over a course of 6 weeks, evidenced Hansen's disease, borderline lepromatous (BL), active. DermPath Diagnostics initially contacted the National Hansen's Disease Program upon diagnosing "superficial and deep granulomatous infiltrate with abundant acid fast bacilli and focal neurotropism" with a perineural association suggestive of Hansen's disease. Subsequent dermatopathology consultation with the National Hansen's Disease Program revealed Polymerase Chain Reaction results and *Mycobacterium leprae* DNA positive confirming the diagnosis of Hansen's disease, in particular, BL type.

The disease is commonly classified according to the Ridley–Jopling classification system—humoral versus cell-mediated type (Ridley & Jopling, 1962). For example, types include indeterminate, tuberculoid, borderline tuberculoid, mid-borderline, BL, and lepromatous (Infectious Disease Epidemiology Section, Louisiana Office of Public Health, 2014). Telephone consultation with the National Hansen's Disease Program ensued. Further clinical examination evidenced increasing hypopigmentation and probable diminished sensation within the patches on the thighs, but no numbness was evident. Pursuant with the program treatment protocol, the patient would remain in our care and receive the prescribed multiple-drug therapy treatment regimen provided by the program. It would be sent to our office and then dispensed from our office to the patient for roughly 2 years. The following laboratory tests were ordered: complete blood count with differential + platelets, Chem 20 including aspartate aminotransferase, calcium, alanine aminotransferase, blood urea nitrogen, creatinine; bilirubin, G6PD, and Hepatitis B and C profile, with plans to repeat, at 1–2 months, the following: complete blood count with differential, AST, and ALT. In addition, these later laboratory tests were to be repeated at 3, 6, 12, 18, and 24 months. Patient education included the following: No blood test for the diagnosis of this disease is available; rather, a skin biopsy is needed; the disease is not very contagious; armadillo contact is the likely source of infection; and based on his skin sample evaluated at the National Hansen's Disease Program, three oral antibiotics were deemed best to treat him—dapsone, minocycline, and rifampin. Additional patient education included the following points: the possibility of a reaction to one or more of the medications and the disease. Risks included, but not limited to, allergic reactions; treatment consequences, such as ENL; and a blue tinge to the skin. Our patient was advised to pursue laboratory tests and contact us at once if any neurological symptom arose, and our office would call him immediately upon our receipt of the aforementioned medications. The initial laboratory results were unremarkable, and the multiple-drug therapy regimen ensued on December 2013. Our patient showed adherence and partnership in his plan of care including attending follow-up visits every 3 months.

Complications

By September 2014, the patient had uneventfully, baring slight anemia without consequences and completed 9 months of the prescribed 24-month treatment protocol, evidencing only a slight cutaneous improvement. One year into treatment, the patient reported slight cutaneous improvement without concerns. Abruptly, within 2 weeks, the patient returned for an episodic office visit complaining of a new rash, with a duration of 1 week, which was red, swollen, and severely painful and distributed on his arms. His self-treatment included 0.1% triamcinolone topical cream to no avail. An additional 4-mm punch biopsy was collected from the newly erupted representative lesion distributed on the left arm. On this occasion, the clinical impression included Hansen's disease T1R reaction versus ENL reaction. Telephone consultation followed again with the National Hansen's Disease Program, and the recommendation included discontinuing the rifampin and starting oral prednisone 40 mg once daily. Once again, our patient's dermatopathology slides were forwarded to the National Hansen's Disease Program for further evaluation. Within 2 weeks, the patient returned to the office and reported that the inflammation (redness and pain) was significantly diminished with the plan of care. DermPath Diagnostics reported "superficial and deep lymphohistiocytic inflammatory infiltrate," whereas Fite stain highlighted clusters of acid-fast bacilli within epithelioid granulomas associated with dermal lymphocytic infiltrate

and consistent with BL leprosy and clinically favored T1R reaction.

However, shortly thereafter, a new lesion erupted on the face, distributed at the right cheek. Additional laboratory tests were collected: C-reactive protein and erythrocyte sedimentation rate. Again, a telephone consultation with the program ensued, and a recommendation to proceed to oral thalidomide was issued, and with it, an arduous protocol including medication availability only through a restricted distribution program, Thalidomide Risk Evaluation and Mitigation Strategy, formerly known as S.T.E.P.S., to include a signed physician–patient agreement, high-risk medication monitoring, and physician enrollment. This recommendation was followed immediately, and the physician pursued the process to provide the patient with thalidomide. The CRP and ESR returned to normal; however, the program consultant was concerned that the collection of these laboratory tests along with the skin biopsy was early in the course of new symptoms and might skew the results. Specifically, she was concerned by the lack of dermatopathological comment regarding neutrophils in the recent punch biopsy histopathological examination, and therefore, the complication of ENL could not be ruled out.

By April 15, 2015, roughly 2 weeks, the patient continued to improve while awaiting thalidomide. Consultants at the program received and evaluated the most recent histopathological slides and determined that the latter could be ruled out and thalidomide could be averted. The clinical goal turned to weaning the patient off the oral prednisone and initiating long-term immunological treatment with oral methotrexate and folic acid.

COMPLICATIONS: T1R REACTION VERSUS TYPE 2 ENL

The incidence of complication in Hansen's disease is related to the immune response mounted by an individual against the pathogen. Two major complications include intricate immunological phenomena: T1R and Type 2 ENL. Each reaction is a distinct consequence and may occur separately and arise at different times in the same patient. As with the disease, the early diagnosis of a reaction complication is paramount if we are to prevent permanent disability. These reactions may present before, during, and after successful appropriate multiple medication therapy is completed (Walker, Saunderson, Kahawita, & Lockwood, 2012). Oral corticosteroids are the first-line treatment, but data are sparse, and as of yet, there is no consensus regarding dose and duration.

T1R represents a delayed hypersensitivity reaction, an immune-mediated episode localized in the skin and nerves (Walker & Lockwood, 2008). Researchers reported that this type of reaction is a leading cause of alteration in nerve function, impairment, and disability; however, roughly 30%–70% of the nerves fully recover with treatment. Dermatopathological characteristics include edema, increased number of dermal lymphocytes, and loss of normal granuloma organization (Walker et al., 2012). As with the aforementioned clinical case, in our patient's course, a T1R is characterized by an abrupt onset of inflammation in the nerves and skin, whereas systemic symptoms such as fever are uncommon. Acute skin lesions become edematous and may ulcerate. Scaling in lesions may signal chronicity and masquerade as psoriasis, dermatophyte infections, and cutaneous T-cell lymphoma.

ENL represents a more grave immunological complication and is more often associated with BL and lepromatous types of the disease. In addition, it should be considered in the differential diagnosis with erythema nodosum and other forms of panniculitis (Walker et al., 2012). Dermatopathological characteristics include dermal and subcutis inflammatory infiltrate. Timing of the skin biopsy is influential. For example, in an acute lesion, typically within 72 hours of eruption, neutrophils predominate, whereas later biopsies evidence fewer but increasing lymphocytes, plasma cells, and histiocytes (Walker et al., 2012). Clinically systemic symptoms are likely, such as high fever, prostration, peripheral edema, transient proteinuria, iritis, episcleritis, lymphadenopathy, organomegaly, and tibial bone tenderness. Thalidomide treatment is very effective in moderate-to-severe cases (Walker et al., 2012). Cutaneously, clinical signs include widespread crops of erythematous, inflamed nodules and papules (superficial and deep), with possible necrosis, ulceration, and pustular and bullous forms. Notably, neuritis may accompany skin manifestations, but often, it is less dramatic when compared with the T1R reaction type of complication (Walker et al., 2012).

Conclusion

The authors presented a compilation of recent clinical experiences in diagnosing and treating a rare disease. Consultants included the world's leading authorities in the diagnosis and treatment of Hansen's disease and its complications. Namely, such authorities included, but were not limited to, the National Hansen's Disease Program, Baton Rouge, Louisiana; Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; World Health Organization; U.S. National Library of Medicine, National Institutes of Health; and Initiative for Diagnostic and Epidemiological Assays for Leprosy. In addition, locally, our recent personal and professional experiences were tremendously motivating and gratifying. Our emphasis in manuscript preparation remained within the United States and centered on our recent experiences during a resurgence of the disease in our community.

Our review of the literature reveals a glaring lack of national awareness regarding the early diagnosis and treatment of this ancient disease. Furthermore, the disease and its complications are rare, thus by a shear lack of numbers, limiting the power of the data thus far collected and analyzed. In each publication reviewed in the preparation

of this manuscript, an author cited the need for more research.

Clinically, health care providers should consider this disease in the differential diagnosis when treating any chronic or recalcitrant skin disorder and rheumatologic disorder. Nondermatology healthcare providers are reminded of the tremendous difference a proper skin biopsy and prompt evaluation by a dermatopathologist can have on a patient outcome. Finally, all health care professionals should please consider taking an hour to view the aforementioned free online course available at www.hrsa.gov/hansensdisease. ■

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