Half a Century in Hiding: A Unique Case of Tuberculoid Leprosy with an Unprecedented Incubation Period

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Patient: Male, 78-year-old
Final Diagnosis: Tuberculoid leprosy
Symptoms: Painless skin lesion
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease
Background: Leprosy, also known as Hansen’s disease, is a neglected tropical disease with low prevalence in the United States. The disease’s long incubation period can cause delayed presentation, and most affected individuals have a history of travel or work in leprosy-endemic regions. The immune response to *Mycobacterium leprae* determines the clinical characteristics of leprosy, with tuberculoid leprosy being characterized by well-defined granulomas and involvement of peripheral nerves. The recommended treatment is a combination of dapsone and rifampin for 12 months.

Case Report: A 78-year-old man with a history of extensive travel to Africa and Asia 50 years ago, presented with a non-tender, non-pruritic, and hypopigmented skin lesion on his left knee. Biopsy results confirmed granulomatous inflammation and the presence of *Mycobacterium leprae*, leading to a diagnosis of tuberculoid/paucibacillary leprosy. The patient received dapsone and rifampin treatment, which resulted in symptom improvement.

Conclusions: The patient’s long incubation period of 50 years between exposure and symptom onset is remarkable and possibly one of the longest reported for tuberculoid leprosy. It emphasizes the importance of considering leprosy in cases with an extensive travel history and long incubation periods. Our patient’s case presented contradictory staining results, suggesting potential sampling variation or a rare mixed leprosy form. Based on his clinical findings, he was diagnosed with tuberculoid leprosy. Early diagnosis and treatment are crucial to prevent irreversible nerve damage and improve patient outcomes. Healthcare providers should be vigilant in acquiring a detailed travel history to facilitate early diagnosis and appropriate management of leprosy cases.

Keywords: Infectious Disease Incubation Period • Leprosy, Tuberculoid • Medical History Taking • *Mycobacterium leprae* • Public Health Surveillance • Global Health • Treatment Outcome

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**Background**

Leprosy is a neglected tropical disease that is rarely seen in the United States, with only about 100-150 new cases every year. Most of the affected people have some work or travel history in leprosy-endemic areas, and they may have acquired the disease there [1]. The long incubation period can lead to a very delayed presentation. Globally, the prevalence of leprosy was 133,802 at the end of 2021, according to statistics collected by the WHO [2]. Globally, about 2-3 million people are estimated to be permanently disabled due to leprosy [3].

The immune response to *Mycobacterium leprae* determines the histopathological alterations in leprosy, which, in turn, determine the clinical characteristics [4]. Tuberculoid leprosy has well-defined granulomas that reach the epidermis and consist of epithelioid cells, multinucleated giant cells, and macrophages, surrounded by a ring of CD4+ T lymphocytes, with the finding of a few or no bacilli [4]. It is characterized by single or few, sharply demarcated hypoesthetic or anesthetic lesions with more intensive involvement of the peripheral nerves [5], whereas lepromatous leprosy has several skin lesions that are smaller in size than those observed in tuberculoid leprosy. They are often distributed symmetrically, with poorly defined borders and no loss of sensation. The lesions can be macules, nodules, or papules, which diffusely infiltrate the skin of the face, leading to the characteristic “leonine facies”. Classically, they have symmetrical nerve involvement, which presents as stocking-glove distribution, which is unrelated to the location of the skin lesions [5].

The recommended treatment, according to the United States National Hansen’s Disease Program (NHDP), is a combination of dapsone and rifampin for 12 months [6]. In 2020, Florida was the top reporter of cases of leprosy out of the total 159 cases in the United States according to the National Hansen’s Disease Program [7].

We report this case because it has a remarkably long incubation period that has not been previously reported in a patient with tuberculoid leprosy.

**Case Report**

A 78-year-old man presented to the Infectious Diseases clinic with a skin lesion on his left knee that was not painful or pruritic (Figure 1). It was stable in size, with a <2 cm plaque that was slightly raised. There was no appreciable extension of the lesion. He scratched at the area repeatedly, which resulted in slight bleeding at one point. He was an active person with an extensive travel history, including significant travel to Africa and Asia while he worked in the Peace Corps about 50 years ago. He had a history of arthritis status post spinal fusion, leading to spinal stenosis and carpal tunnel syndrome status post-surgical release on the left side, which result in numbness and paresthesias of the extremities, but no focal deficits, CKD stage 3, and various minor skin lesions such as actinic keratosis that were treated in the past. After extensive history taking it was seen that he had never been exposed to armadillos by hunting or eating.

![Figure 1](image1.png)

**Figure 1.** Picture of the skin lesion at initial presentation. The arrow points at the tiny patch of hypopigmented skin, also circled in red.

![Figure 2](image2.png)

**Figure 2.** The granulomas are composed of macrophages with greyish cytoplasm, variable foamy change (“Virchow cells”) and varying numbers of large vacuoles (hematoxylin and eosin, 40×).
On general examination, the patient was vitally stable. On systemic examination, a slightly hypopigmented papule was noted on the inner surface of his left knee. He also had residual actinic keratosis and regions of sun damage on his arms and legs. There were no significant findings documented on the peripheral examination of the nerves or on hot and cold testing.

His clinical and exposure history suggested that it could be an environmental non-tuberculous mycobacterium (NTM). To confirm our diagnosis, we biopsied the lesion and sent it for testing. The histopathology examination (Figure 2) of the lesion showed that within the dermis there was prominent granulomatous inflammation consisting of epithelioid histiocytes and associated small, mature lymphocytes. Focal admixed neutrophils were present. Polarizable foreign material was not seen. The FITE stain (Figure 3) demonstrated innumerable positive mycobacteria clustered in small granules and as single organisms. Foamy macrophages were seen in the AFB stain, Figure 4. The fungal PAS stain was negative. Prominent granulomatous infiltrate with minimal lymphocytic inflammation was seen (Figure 5).

Based on the histopathology report, a diagnosis of Hansen’s disease was made, and the patient was started on dapsone 100 mg PO (per oral) OD (once daily) and rifampin 300 mg PO (per oral) BD (twice daily) for 12 months based on the guidelines of the United States National Hansen’s Disease Program (NHDP). He was noted to have a grade of 0 on the WHO disability grading scale for leprosy. [8] On follow-up visits, he noted a slight decrease in the irritability of the lesion.

The patient was seen to have tuberculoid/paucibacillary leprosy with a positive Mycobacterium Leprae PCR. We put him in contact with the US Department of HHS’s National Hansen’s Disease Program.

He was followed until the antibiotic duration ended and was seen to not have any adverse effects due to the drugs. No extension of the antibiotic duration was needed as his symptoms resolved completely with therapy.
Discussion

We hypothesize that the patient’s extensive travel and work history, involving endemic regions like Asia and Africa in the past, is what led to his symptoms. It is not possible to confirm the source of the infection, but this explanation is the most plausible. He had a long incubation period, about 50 years. His carpal tunnel could be due to nerve enlargement caused by Mycobacterium leprae, known to preferentially attack the “cold” peripheral nerves.

Other possible sources of infection in the United States of America could be exposure to armadillos, but the patient firmly denied any contact with armadillos – hunting or eating – thereby making it less likely. Another possibility could be exposure to someone in the States who has leprosy, as it is a communicable disease, but he denied contact with anyone with diagnosed leprosy. Furthermore, there are very few cases of leprosy detected in the USA, making exposure here less likely.

Another possibility is that the patient ignored the earlier findings and hence remained undiagnosed for such a long time. However, he denied the presence of any long present symptoms.

Leprosy is caused by infections with Mycobacterium leprae and Mycobacterium lepromatosis, which are both slow-growing bacteria with an incubation period of 5-20 years, depending on their clinical subtype. Transmission occurs via droplets during close and frequent contact with untreated cases.

In our patient, there is an extensive travel history to endemic regions followed by a long incubation period of 50 years. To our knowledge this is the longest reported incubation period for a case of tuberculoid leprosy.

In our patient, another complicating factor to note was that there were contradicting findings on AFB and Fite-Faraco staining. Fite-Faraco looks like a tuberculoid pole implying tuberculoid leprosy, and AFB staining shows foamy macrophages which are more characteristic of a lepromatous pole. Such situations are rare and require further investigation and clinical correlation. There are a few possible explanations for the varying poles seen on the tests; 1) sampling variation; 2) mixed leprosy; 3) technical errors.

Since the samples are typically small, the findings might not represent the entire spectrum of the disease. The findings are also dependent on user error. Mixed forms of leprosy are also seen rarely which show the characteristics of both the poles – tuberculoid and lepromatous. A case was described by Roxburgh A in which the patient had both tuberculoid as well lepromatous findings seen. Variation in staining techniques as well as the interpretation of results can also potentially lead to discrepancies.

Based on all the findings and the clinical presentation we ruled in the favor of tuberculoid leprosy, based on the single skin lesion and the sensory nerve damage (presence of numbness) with no nerve thickening or motor nerve damage (for example, no foot drop). It is an atypical presentation.

A case of lepromatous leprosy was reported in Europe in which a Thai lady was seen to have a 30-year incubation period. She was diagnosed on the basis of the presence of all the cardinal signs of the WHO diagnostic criteria. Another case with lepromatous leprosy was seen to have an incubation period of 50 plus years. The man lived in Australia and had worked in close contact with patients with leprosy about 50 years ago and had never traveled overseas. Only non-human primates have been seen to have such a long incubation period. It is extremely rare in humans.

The diagnosis of leprosy is delayed in developed countries, and hence an extensive travel history should be acquired as it can have a long incubation period and can present several years post-travel. It is particularly important to diagnose and start treatment early, as otherwise the damage can become irreversible.

Leprosy is diagnosed using the WHO’s list of cardinal signs; 1) bacilli on slit-skin smear examination along with loss of sensation in the hypopigmented skin lesion 2) enlarged peripheral nerve with loss of sensation 3) weakness in the muscles supplied by that nerve. The presence of even one of the mentioned cardinal signs is enough to establish a diagnosis of leprosy. Our patient has one, bacilli on a slit-skin smear examination and was hence treated with dapsone and rifampin as recommended by the guidelines, and he showed improvement.

Based on the physical disabilities seen in patients with leprosy, the WHO created a grading system. Grade 0 has no disability (no anesthesia) and no visible deformities. Grade 1 has sensory losses that lead to a defect in protective sensations on their eyes, hands, and/or feet, but no visible deformities. Grade 2 has the addition of visible deformities to a defect in protective sensations. Our patient had a disability grade of 0.

The treatment regimen for this patient was decided as per the United States National Hansen’s Disease Program, in which tuberculoid leprosy is treated with dapsone and rifampin for 12 months. Lepromatous leprosy is treated with dapsone, rifampin, and clofazimine for 24 months.

Since the treatment regimen for these drugs is long (12 months at least), there is a chance that adverse effects can occur. Dapsone can lead to various adverse effects like peripheral neuropathy, abdominal pain, anorexia, and headache. Patients can also develop dapsone syndrome, which usually develops...
after 2-6 months of dapsone therapy and classically manifests as fever, rash, and hepatitis. The clinical picture can resemble infectious mononucleosis, with blood work showing peripheral eosinophilia and elevated liver enzymes. If not treated appropriately, it can be life-threatening [19-21]. Rifampin is in general considered to be a well-tolerated drug. However, it has dose-dependent adverse effects like orange discoloration of body fluids, constipation, and asymptomatic hepatitis, as well as dose-independent adverse effects, including hypersensitive reactions like urticaria, thrombocytopenia, and renal failure. Many of these adverse effects resolve after discontinuation of the drug [22-25]. Luckily, our patient reported development of no adverse effects.

There are other diseases that present with skin manifestations that were also on the differential for our patient. Africa is home to Mycobacterium ulcerans, which can also cause skin manifestations, and our patient had a history of travel to Africa. It has 3 clinical stages of the lesions: pre-ulcerative, ulcerative, and healed. The pre-ulcerative lesions can resemble the lesions seen in our patient – single painless subcutaneous lesion that slowly expands over time – but the skin over it would eventually slough off, leading to the formation of an ulcer. Most of the skin lesions present as ulcers and not as nodules or plaques [26]. In addition, it is not endemic to the USA and has a comparatively short incubation period of 4-5 months, making it less likely [27].

Cutaneous tuberculosis occurs due to chronic infection by Mycobacterium tuberculosis, Mycobacterium bovis, and occasionally by Calmette-Guerin bacillus. It has numerous manifestations that depend on the host’s immunity and the site of infection. Some of them are painless [28]. It is diagnosed by a skin biopsy, which is evaluated for AFB and then cultured at low temperature to detect growth of Mycobacterium tuberculosis [29-31].

The cutaneous manifestations of Nocardia generally include mycetomas and discharging sinuses [32]. It is commonly seen after penetrating trauma from a contaminated object or exposure of a pre-existing wound to contaminated soil or water [33]. It occurs more commonly in patients who are immunocompromised and is likely to disseminate to affect distant parts of the body [34]. The localized lesions are generally painful and appear as nodules or ulcerations and less commonly as papules, pustules, or subcutaneous abscesses [35]. Our patient had painless lesions.

Carpal tunnel syndrome often occurs in patients with chronic kidney disease (CKD), especially in patients with AV fistula. Furthermore, it is bilateral, which adds to the bias that CKD is the cause, as it typically has bilateral involvement [36]. The important point to note is that the left side had more severe carpal tunnel compared to the right, based on EMG studies. This confirms that leprosy is more likely than CKD to be the cause.

Neuropathy can often be missed as a clue to diagnosing leprosy in developed countries, as several other causes are more common and hence would be higher on the differential. The painless, hypopigmented skin lesion helped finalize the diagnosis and suggest the presence of leprosy. Patients may undergo several decades of subclinical features and present with symptoms after international migration into geographic regions where the disease is considered to be eradicated [37]. This shows that a thorough surveillance for the presence of such diseases, in the modern world where all geographic locations are very interconnected, should always be done.

A delayed diagnosis could lead to an adverse outcome and delay the start of treatment, increasing the risk of irreversible neuropathic damage. Therefore, an extensive travel history should be taken to ensure early diagnosis and early treatment, leading to better patient outcomes.

Conclusions

Although leprosy is not commonly seen in the developed countries, it should be kept on the differential as it can present several years after initial infection. A thorough travel history and history of exposure can be very helpful in early diagnosis and hence in starting the treatment early, improving patient health outcomes and reducing long-term complications.

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References:

18. World Health Organization. Guidelines for the Diagnosis, Treatment and Prevention of Leprosy. Published: October 6, 2018. Available at: https://www.who.int/publications/i/item/9789240726381