CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

D Is for Delay

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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N Engl J Med 2014;371:2218-23.
DOI: 10.1056/NEJMcps1212211

A 47-year-old homeless man presented to a local emergency department with intermittent pain and a pins-and-needles sensation in his legs. One month earlier, paresthesias had developed in his toes, which spread gradually to his shins. He did not have lower back pain, muscle weakness, fever, chills, weight loss, bowel or bladder dysfunction, nausea, vomiting, or fatigue.

Pain and paresthesias of the bilateral lower extremities are characteristic of a polyneuropathy. The basic approach to diagnosing a peripheral neuropathy includes establishing the pattern of nerve involvement and the time course, discerning motor and sensory involvement, and searching for evidence of systemic disease. The most common causes of polyneuropathy are diabetes mellitus and alcohol abuse (through direct toxic effects or associated nutritional deficiencies, such as vitamin B_{12} deficiency). Since the common polyneuropathies evolve over a period of months to years, the ascending symptoms over a 1-month period raise the possibility of a more rapid and progressive neuropathy such as acute inflammatory demyelinating polyradiculoneuropathy (the Guillain–Barré syndrome) or neuropathy due to vasculitis, heavy-metal toxicity, acute porphyria, or a paraneoplastic syndrome. There are no back-pain or bowel or bladder symptoms to suggest the presence of a myelopathy or radiculopathy.

The patient had a 33-year history of intravenous heroin use and was a current user. He had hepatitis C virus (HCV) infection and hypertension. He was taking no medications. The patient had a smoking history of 52 pack-years and reported rare alcohol intake. He was not sexually active. There was no family history of neuropathy.

On physical examination, the patient appeared chronically ill. He was alert and was oriented to person, place, and time. He was afebrile, with a blood pressure of 170/110 mm Hg, a pulse of 68 beats per minute, and a respiratory rate of 20 breaths per minute. The cardiac, pulmonary, abdominal, and skin examinations were normal. Neurologic examination revealed no abnormal cranial-nerve findings, muscle strength of 5 out of 5 bilaterally, and normal deep-tendon reflexes. He had an unsteady gait and limited ambulation owing to pain, and there was decreased sensation of pinprick, light touch, and temperature on the lower extremities bilaterally.

The impaired sensory responses on neurologic examination are compatible with a distal sensory neuropathy that predominantly involves the small, unmyelinated nerve fibers. The absence of impaired vibration sense or proprioception makes diseases of the large, myelinated nerve fibers or dorsal column less likely. The absence of hyperreflexia, increased tone, sensory level, and distal motor weakness argues

against a compressive myelopathy (e.g., epidural abscess caused by intravenous drug use).

The patient's chronically ill appearance may signal a systemic disorder. HCV-related cryoglobulinemia can cause a vasculitic neuropathy. However, skin lesions, which are commonly associated with cryoglobulinemic vasculitis, were not noted. His long smoking history increases the risk of cancer and supports the consideration of neuropathy due to a paraneoplastic disorder. His intravenous drug use puts him at risk for human immunodeficiency virus (HIV) infection, which is also associated with a peripheral neuropathy.

The white-cell count was 9000 per cubic millimeter, the hemoglobin level 10.3 g per deciliter (normal range, 11.2 to 14.1), and the platelet count 241,000 per cubic millimeter. The mean corpuscular volume was 98 fl. The vitamin B_{12} level was 965 pg per milliliter (710 pmol per liter), and the serum folate level 14.6 ng per milliliter (30 nmol per liter). Electrolyte and aminotransferase levels were within normal limits. Testing for HIV, rapid plasma reagin, and cryoglobulins and urine and serum toxicologic screening were negative.

The patient was considered to have an idiopathic peripheral neuropathy and was discharged from the emergency department with prescriptions for gabapentin, amitriptyline, and morphine. A gastroenterologist prescribed peginterferon alfa-2b and ribavirin for the HCV infection, and the primary care provider prescribed labetalol, lisinopril, and clonidine for hypertension. The patient's pain progressively worsened. Needle electromyography, performed 6 months after he first presented to the emergency department, revealed a very severe axonal sensorimotor polyneuropathy in the lower extremities bilaterally. Nerve-conduction studies showed that sural sensory responses and bilateral peroneal and tibial compound muscle action potential were absent. The patient was referred for a nerve biopsy and was prescribed oxycodone (in place of morphine).

Testing for cryoglobulinemia involves challenging logistics in terms of handling and processing the sample, so a false negative result is possible. The nerve-conduction studies point to an axonal neuropathy, which characterizes the majority of peripheral neuropathies. The high-normal vitamin B_{12} level and normal blood smear make vitamin B_{12} deficiency unlikely. Measurement of thiamine levels and empirical thiamine repletion would also be reasonable, although the patient reports rare alcohol intake. An underlying cancer remains a major concern. Serum and urine electrophoresis should be performed, especially in light of his anemia, although paraproteinemic neuropathies are usually characterized by demyelination rather than by axonal degeneration. The toxicologic studies were negative, but I would confirm that the screening included tests for heavy metals such as lead and arsenic, and I would question the patient about any possible environmental exposures.

Nine months after the patient's first visit to the emergency department, pruritic, violaceous plaques developed in a photodistributed manner on the dorsal aspects of the arms and on the legs and upper chest. Empirical treatment was prescribed serially in the general medicine clinic for scabies (permethrin cream), then tinea corporis (topical and oral ketoconazole), then cellulitis (bacitracin ointment, oral levofloxacin, and intravenous vancomycin), and then a possible allergic contact dermatitis to bacitracin (fluocinolone acetonide ointment). A sural-nerve biopsy revealed axonal degeneration and extensive loss of large and small myelinated and unmyelinated fibers.

Superficial plaques are commonly explained by psoriasis or eczema, which are not associated with neuropathy. Conversely, entities associated with plaques — particularly deep, firm plaques without scale — and neuropathy include vasculitis, sarcoidosis, amyloidosis, cancer, and indolent infections such as fungal infections or tuberculosis. None of these disorders are consistent with the nerve-biopsy findings in this patient. Although previous testing for cryoglobulins and syphilis with the use of a rapid plasma reagin test was reported to be negative, I would repeat these tests (with careful attention to correct processing of the specimen for cryoglobulins); a skin biopsy would also be appropriate. Long-term exposure to arsenic causes scaling lesions and symmetric polyneuropathy, but the latter typically precedes the former.

Repeat testing for HIV antibodies was negative, as was a rapid plasma reagin test, tests for anti-Ro, anti-La, anti-Sm, and anti-RNP antibodies, and a

test for cryoglobulins (with the sample delivered to the laboratory at body temperature). Blood cultures were also negative. The doses of oxycodone and gabapentin were increased. The patient began to walk with a limp. Despite six negative tests for serum cryoglobulins during this time, strong clinical suspicion led to a presumed diagnosis of cryoglobulinemia.

Although the patient's HCV infection made cryoglobulinemia a reasonable concern, this diagnosis appears to be extremely unlikely at this point, given the multiple negative tests. Evaluation is warranted for evidence of other vasculitides, including repeat physical examination with attention to the joints, urinalysis, chest radiography, and skin biopsy.

Eight months later (17 months after his initial presentation), the patient returned to the emergency department with weakness in the lower extremities, diarrhea, dehydration, rash (consistent in distribution and appearance with his prior rash), and new leg ulcerations, which he attributed to scratching. He did not have hematochezia, abdominal pain, episodes of constipation or abdominal bloating, nausea, or vomiting. Stool samples were negative for *Clostridium difficile* toxin, leukocytes, ova and parasites, and occult blood. He was treated with loperamide, with subsequent improvement in his diarrhea. Oral levofloxacin and intravenous nafcillin were administered for possible infection of neuropathic ulcerations. Owing to weakness, he was discharged to a nursing home.

The diarrhea may signal gastrointestinal involvement of whatever process has caused the neuropathy and skin lesions. Conditions such as vasculitis (in particular, polyarteritis nodosa) and amyloidosis (which may cause diarrhea by means of direct luminal infiltration or autonomic insufficiency) remain possible. Inflammatory bowel disease can have varied cutaneous manifestations (e.g., pyoderma gangrenosum or erythema nodosum), but severe neuropathy is not characteristic. Nutritional deficiencies are still possible, especially given the patient's homelessness. Specifically, niacin deficiency should be considered in the presence of diarrhea and a rash; dementia, however, rather than neuropathy, is the typical neurologic manifestation of pellagra.

During his 16-week nursing home stay, the patient had poor oral intake and declined to take medications. He had violent outbursts that were uncharacteristic of his prior behavior; he accused a nurse of stealing his pen and, on another occasion, repeatedly hit the elevator with a fire extinguisher in an attempt to leave the facility. He received a diagnosis of depression and was prescribed fluoxetine, without appreciable improvement in his behavior. At the time of discharge, the patient had limited and painful ambulation. He continued taking labetalol, lisinopril, and clonidine.

During the next 2 years, the patient was admitted to the hospital on five occasions: once after police found him aimlessly wandering busy streets and four times for erythema in the lower extremities that was presumed to be cellulitis; the episodes of presumed cellulitis were managed with numerous antibiotic agents. He continued to report occasional loose stools, for which he was given loperamide. The patient was noted to be confused during his hospital stays. Eventually, his leg pain progressed to the point that he was confined to a wheelchair.

The patient has progressive neuropathy and continues to have confusion. A unifying diagnosis that could explain these findings as well as his rash and diarrhea should still be sought. It is nearly inconceivable for a cancer to have gone undetected for more than 2 years with such profound systemic manifestations. Chronic infections that involve the central nervous system include syphilis, Whipple's disease, HIV infection, and Lyme disease. All but Whipple's disease are associated with neuropathy, but Whipple's disease would be most likely to cause diarrhea. Retesting for syphilis, HIV infection, and Lyme disease is indicated, in case the results of earlier tests were falsely negative. Metabolic and nutritional derangements, such as niacin deficiency, remain part of the differential diagnosis and warrant assessment.

After a 4-week course of clindamycin for his fourth episode of suspected cellulitis, the patient returned to the emergency department because of an increased number of loose stools (10 to 15 a day), abdominal pain, nausea, and vomiting. He was noted to be uncooperative and inconsistent in reporting symptoms. He was treated symptomatically for gastroenteritis but returned to the emer-

gency department 1 week later with persistent diarrhea. Computed tomography (CT) revealed colonic-wall thickening, and stool samples showed *C. difficile*. The patient was discharged with a prescription for oral metronidazole. Six days later, he returned with increasing abdominal pain. A repeat CT scan showed free air in the nondependent portion of the abdomen. After exploratory laparotomy, which revealed a perforation of the large intestine, the patient underwent subtotal colectomy and ileostomy. Postoperatively, he continued to take oral metronidazole. Examination of the colectomy specimen showed no evidence of cancer or infectious organisms.

The patient returned to the emergency department 13 months later (5 years after his initial presentation) with persistent diarrhea and rash. He was treated with intravenous vancomycin for cellulitis. The dermatology service was consulted. A skin-biopsy specimen showed features suggestive of psoriasis and eczema but was considered to be nondiagnostic. Repeat stool samples for *C. difficile* were negative. Clobetasol propionate ointment was prescribed, and the patient was seen periodically in the clinic over the next 2 years, with no change in treatment. The photodistributed rash persisted (Fig. 1) and at some point during that period included a well-marginated eruption, forming a band on the neck (Fig. 2).

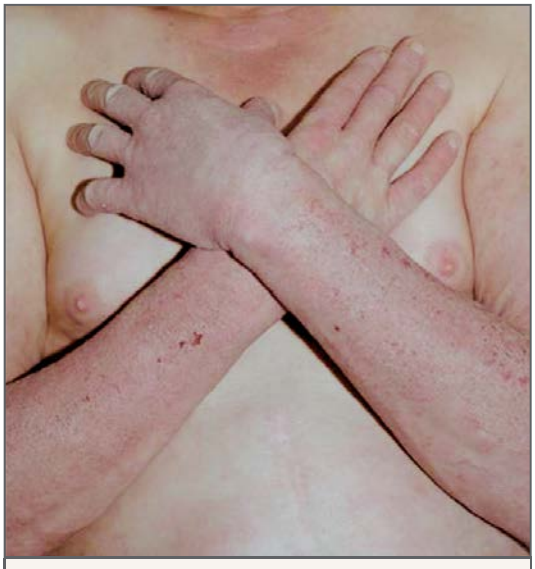

Figure 1. Symmetric, Photodistributed Erythema with Overlying Hyperkeratosis.

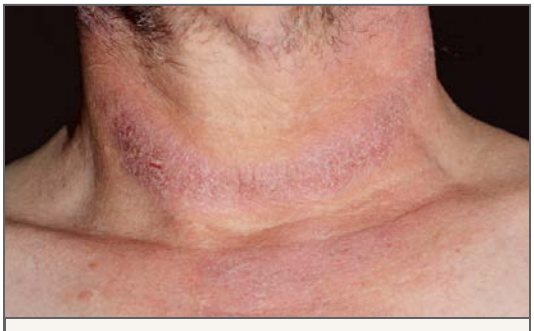

Figure 2. A Well-Demarcated Erythematous Eruption in the Distribution of a Necklace.
A hallmark clinical sign of pellagra is Casal's necklace — an eruption on the front of the neck extending into the region of cervical dermatomes C3 and C4.

The *C. difficile* infection is presumably a consequence of the patient's antibiotic treatment and is probably responsible for his colonic perforation. The appearance of a bandlike rash around his neck provides a new clue to a unifying diagnosis for his other symptoms and signs. Taken together, dermatitis (especially in sun-exposed areas), dementia, and diarrhea suggest pellagra (niacin deficiency), especially given social factors predisposing the patient to poor nutrition. Peripheral neuropathy has also been described in patients with pellagra. Another possibility is that he has niacin deficiency in combination with a deficiency of another micronutrient, such as thiamine.

A serum niacin level was undetectable. No other micronutrient levels were assessed, and no dietary history was obtained. Treatment with oral niacin at a dose of 500 mg daily was initiated. On evaluation 3 months later, the patient's rashes had nearly completely resolved, his cognition was normal, and he had had no further violent outbursts and reported no diarrhea. His advanced neuropathy, however, persisted.

COMMENTARY

Pellagra (or "rough skin," from the Italian *pelle agra*) is rare in the United States, but it remains an important problem in developing countries. This condition results from inadequate dietary intake

of niacin and is characterized by "the four Ds": diarrhea, dermatitis, dementia, and death.[1,2] The mechanism by which niacin deficiency leads to such severe multisystem failure is poorly understood. Pellagra develops in the context of malnutrition, including restricted diets and alcohol abuse.

Patients with pellagra can have a wide range of neuropsychiatric manifestations, such as irritability, anxiety, delusions, hallucinations, apathy, spastic paresis, fatigue, depression, myelitis, and peripheral neuropathy of the upper and lower extremities.[3] Since the neuropathy in this patient persisted despite niacin replacement, it is difficult to say whether it was related entirely to niacin deficiency or might have been associated with other vitamin deficiencies. However, there have been other case reports of neuropathy attributed to pellagra that did not improve despite niacin replacement.[4]

The dermatitis of pellagra involves sun-exposed skin in a bilateral and symmetric pattern.[2] The characteristic and prominent eruption can occur on the dorsum of the hands, the V-area of the neck, the face, and exposed skin on the legs and feet.[5] The rash may resemble a sunburn with erythema, or it may be characterized by hyperpigmentation, thickening, dryness, and roughness.[6,7] Pain may also develop owing to fissures and excessive dryness.[8] One of the hallmark clinical signs is an eruption on the front of the neck extending into the region of cervical dermatomes C3 and C4, simulating a necklace (Casal's necklace).[9]

Approximately half the patients with pellagra have gastrointestinal manifestations.[10] The diffuse inflammation and atrophy of the mucosal surface of the gastrointestinal tract result in diarrhea. Anorexia and malabsorptive diarrhea lead to malnutrition and eventual cachexia.

Whereas this patient had resolution of many of his symptoms with niacin supplementation alone, patients with pellagra should also receive a high-protein diet and B-complex vitamins, since they frequently are malnourished and have other vitamin deficiencies. The response time varies according to the severity of the disease, but clinical improvement may be seen within a few days after the start of treatment.

Although pellagra is a prototypical nutritional deficiency with a well-defined tetrad of clinical manifestations, its recognition can be impeded by cognitive errors and systems factors, as occurred in the present case. The classic symptoms and signs of niacin deficiency typically evolve at different intervals over time, rather than appearing simultaneously, making it harder for the clinician to see the pattern and apply diagnostic parsimony.[11] In the present case, neuropathy dominated the early presentation; the focus on this condition may have diverted attention away from the correct diagnosis of pellagra even as its typical manifestations emerged.

In the absence of pattern recognition, clinicians tend to think of each issue separately and develop reasonable working alternative diagnoses. However, once there is diagnostic momentum (the tendency for a particular diagnosis to become established over time across multiple providers without adequate evidence or verification), reframing the situation in each new encounter becomes more challenging, and previous solutions (in this case, antibiotic treatment for recurrent episodes of presumed cellulitis) become engrained.[12] These patterns of care can result in adverse outcomes (in this case, *C. difficile* infection with attendant complications) and a long delay in diagnosis.

Systems-level issues created additional challenges in this case. Vulnerable patients, such as this homeless man with impaired mental status who had difficulty providing information and following recommendations, require continuity and coordination of care.[13] The simple provision of empirical vitamin supplementation could have prevented tremendous suffering and expense. Fragmented care from multiple providers undoubtedly created additional barriers to recognizing the neuropsychiatric complications, dermatitis, and diarrhea that developed over a period of years in this patient. Taken together, these factors unfortunately contributed to a fifth "D" in this case of pellagra: delay.

Dr. Saint reports receiving fees for board membership from Doximity and Jvion. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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