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Case Report

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"The Dizziness is Unnerving": Monoclonal gammopathy of unknown significance presenting as severe neuropathy: A case report

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Abstract

Neuropathic pain is common and is one of the most disabling symptoms of many disease states. This case study highlights a 59-year-old female patient who presented with severe peripheral neuropathy and fainting episodes. Initial treatment provided little relief, so the patient returned to the office, as the dizziness she was reporting had gotten significantly worse. After a significant work up over multiple months, the medical care team diagnosed the patient with monoclonal gammopathy of unknown significance (MGUS). This was done through a CT guided bone marrow aspirate and biopsy that showed a high plasma cell count. The only reason this test was ordered was because a wide differential diagnosis was maintained throughout the patient's encounter with the medical team, allowing for flexibility in testing and treatment when the initial approach failed to work. This paper aims to highlight the purpose of a wide differential when treating patients with neuropathic pain syndromes, especially with severe symptoms including autonomic dysfunction. The possibilities of a differential are highlighted in the paper through a review of the literature on the presentations of neuropathic pain syndromes. This case highlights how a wide differential may have prevented a patient with peripheral neuropathy from developing further sequela of her disease state.

Keywords: peripheral neuropathy, neuropathic pain, dizziness, plasma cell dyscrasia, differential diagnosis

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Introduction

Neuropathic pain is a widespread and disabling condition. Like any pain syndrome, neuropathic pain decreases the quality of life and increases the risk of suicidal ideation (31). Because all sensation is carried by nervous fibers, there is a widespread variance in the distribution and type of the loss of sensation. Neuropathic pain is common and is one of the most disabling symptoms of many disease states (1).

Case Presentation

Our patient was a 59-year-old female with a chief complaint of severe peripheral neuropathy and fainting episodes. She had a significant medical history of lumbar back disease with sciatica, cerebral infarction, meningioma, peripheral vascular disease (PVD), migraines, neurological gait disorder, hypertension (HTN), hyperlipidemia (LDL >70), elevated hemoglobin A1c (HbA1c), and tinnitus. She had been referred to the outpatient neuroscience center for her severe peripheral neuropathy, characterized by paresthesia in a stocking and glove pattern. Based on her prior history, it was initially assumed that the paresthesia was secondary to a multifactorial

process of small vessel damage of the peripheral and autonomic nervous system. Her physical exam was remarkable for bilateral loss in the hands and feet of vibration, pinprick, and some fine touch sensation. The loss ascended to the levels of the shoulders in the upper extremities and the tibial tuberosity in the lower extremities. She did not have evidence of motor weakness. On orthostatic testing, the patient complained of increased "dizziness," although her blood pressure measurements and heart rate did not support this claim. Based on these initial findings, HbA1c, thyroid stimulating hormone (TSH) level, and vitamin B12 level were ordered and found to be within normal ranges. The patient was set up for electromyographic conduction studies but was unable to get the testing for several months. She was prescribed pregabalin (100 milligrams, three times a day) for symptomatic treatment while the cause was under investigation.

Return Visit

On return visit to the office, the patient reported continued pain in her back and peripheral nerves. She experienced some improvement of symptoms with the use of pregabalin. Nevertheless, due to her worsening and disabling "dizziness" and negative laboratory testing, it was determined that a broader differential should be discussed. This included several B vitamin deficiencies, autoimmune diseases, infections of the liver, sarcoidosis, and potentially cancer.

Tests ordered included: Vitamins (B1, B6, B9), Antinuclear Antibody Screen with reflex to Antinuclear Antibody Complete, Angiotensin-1-Converting Enzyme, Hepatitis Acute Panel, Methylmalonic Acid, Rheumatoid Factor, and Sjogren's Antibody. Serum protein electrophoresis and urine protein electrophoresis were also obtained. While these are much more rare causes of peripheral and autonomic neuropathies, this is the basic laboratory investigation per the AANEM (2).

Diagnosis

The serum protein electrophoresis (SPEP) showed two monoclonal proteins quantified at 0.84 g/dL and 0.19 g/dL, leading to a hematology/oncology referral for further testing. The hematologist/oncologist SPEP/Immunofixation testing of the serum found two IgA Lambda monoclonal proteins quantified at 0.80 g/dL and 0.16 g/dL. Serum kappa-free light chains (FLCs) were 17.01 mg/L, and lambda FLCs were 26.54 mg/L, resulting in a kappa/lambda ratio of 0.64. Beta-2 microglobulin was 2.5 mg/L. IgG was 628 mg/dL, IgA was 1044 mg/dL, and IgM was 65 mg/dL.

To rule out amyloidosis, the patient underwent a CT-guided bone marrow aspirate and biopsy. The pathology report of the aspirate showed Plasma cells at 7% (normal <5%). The high plasma cell count led to the diagnosis of monoclonal gammopathy of unknown significance (MGUS, Non-IgM Subtype), which was determined to be the main cause of the patient's neuropathic pain and autonomic dysfunction. She currently is following up with neurology, cardiology, and hematology/oncology for monitoring of her symptoms plus symptomatic treatment to ensure that she does not worsen.

Discussion

This paper highlights the importance of a wide differential when thinking about neuropathic pain syndromes, especially with severe symptoms including autonomic dysfunction. Peripheral neuropathy can be due to a wide variety of disorders, or idiopathic in up to 40% of patients (3). Neuropathies are commonly sensory but can also involve motor issues loss (3). This paper focuses mainly on sensory loss but does not negate the severe cases in which motor and autonomics are also affected. The sensory neuropathies cause gait ataxia by damaging A-delta myelinated nerve fibers leading to impaired proprioception. The most common causes are paraneoplastic and Sjogren syndrome, but idiopathic forms are also seen (24, 25). Mononeuritis multiplexes involve multiple individual nerves, often in the setting of vasculitis, presenting with patchy asymmetric numbness and weakness (26). Polyradiculoneuropathies present acutely and are often due to inflammatory immune responses, with Guillain-Barre syndrome (GBS) being the most common (27).

Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) occurs in about 50% of all patients with type 1 and type 2 diabetes mellitus (T1DM and T2DM) and in about 15% of patients with prediabetes (1, 4, 30). DPN is one of the first differentials considered and is the most prevalent type of peripheral neuropathy. It is most common in patients who take insulin to treat T1DM (3). The risk of neuropathy in T1DM patients is proportional with the rate of correction regarding HbA1c levels: There is a 20% risk associated with a 2-3% decrease in HbA1c levels over 2-3 months, and an 80% risk with a 4% decrease in HbA1c levels over 2-3 months (5). Furthermore, aggressive glycemic control can decrease the rate and progression of neuropathy in T1DM patients but not in T2DM patients, indicating a multifactorial issue in which hyperglycemia is not the only metabolic cause (6). This presents clinically with a paradoxical numbness with exquisite sensitivity, which can be debilitating for patients experiencing these symptoms. Numbness often leads to falls, and neuropathy is one of the three main risk factors for falls in patients with diabetes (28).

Toxic and Nutritional Neuropathies

Chemotherapy-induced neuropathy is an increasing issue due to the increasing rates of cancer survivors (30). It has been shown to impact more than 30% of patients that receive potentially neurotoxic agents with the highest prevalence in platinum-based drugs, taxanes, and vinca alkaloids (11). Coasting is often seen with chemotherapy-induced neuropathy, where neuropathy can progress for up to 3 months after discontinuation of the drug (30). This is the second most prevalent form of peripheral neuropathy.

Heavy alcohol use in chronic alcoholics is also associated with neuropathy (12). Vitamin B1 deficiencies are an important

consideration in alcoholics or patients who are malnourished. This can result in subacute progressive axonal sensorimotor neuropathy, along with other cardiovascular and cognitive problems (13).

Vitamin B12 deficiency is commonly seen in general practice and is known to present with subacute combined degeneration (33). This is a deterioration of the corticospinal tract and dorsal columns of the spinal cord that results in an impairment of vibration sense and an ataxic gait but can also be associated with neuropathy (34).

Imbalances with vitamin B6, copper deficiencies, zinc overloads, and vitamin E deficiencies have also been shown to result in cases of neuropathy (14-17). Certain antibiotics, specific antiarrhythmic drugs, heavy metals, and organic solvents have all been linked to toxic neuropathies as well (2).

Cryptogenic sensory neuropathy

The diagnosis of cryptogenic sensory neuropathy (CSN) is made by excluding other neuropathic etiologies (2). Metabolic syndrome, obesity, and prediabetes are all associated risk factors for CSN (6). Diet and exercise have been shown to improve symptoms, but many antioxidants have failed to show efficacy in past early-stage clinical trials (8-10).

Inherited neuropathies

Inherited neuropathies can be distinguished by their early onset compared to the previous neuropathies discussed (2). Charcot-Marie-Tooth (CMT) is the most common form of inherited neuropathy and presents with pes cavus, hammer toes, scoliosis, muscle weakness, and variable tremors. The classic CMT phenotype presents before 20 years of age, while infantile forms can be fatal and have a variety of presentations all beginning under 2 years of age (22).

Familial amyloid neuropathy (FAN) is another rare case of inherited neuropathy that is life-threatening. FAN is caused by mutations in 3 genes: transthyretin, apolipoprotein A1, and gelsolin. These mutations destabilize the proteins and lead to amyloid deposits in peripheral nerves. FAN often presents with early autonomic issues, bilateral carpal tunnel syndrome, cardiomyopathy, and an indicative family history (23).

Monoclonal Gammopathy

The most common types of monoclonal gammopathy are that of uncertain significance (MGUS), multiple myeloma (MM), and Waldenstrom Macroglobulinemia, with a prevalence of 3.5% in patients over 50 years of age (3, 18, 35). MGUS can be subdivided into IgM, non-IgM, or light chain MGUS: Non-IgM MGUS has a 1% annual increase in risk progression to MM, with important factors being the size of M protein, and level of immunoglobulin (19, 35). Given this risk, a thorough investigation for neoplasm is necessary (35). In patients with MM, neuropathy is present in about 12% of patients at presentation, and almost 75% of MM patients will go on to develop neuropathy throughout the course of the disease. Treatment includes stem cell transplantation and combination chemotherapy for patients without autonomic dysfunction (20). In about 15% to 20% of patients with frequent autonomic dysfunction, light chain amyloidosis can result in progressive neuropathy (2). IgM MGUS is more common to result in peripheral neuropathy (35). A nerve conduction study is the gold standard for the diagnosis of distal acquired demyelination syndrome. Approximately 25–30% of patients with IgM monoclonal gammopathy-associated peripheral neuropathy have moderate disability at 10 years (37).

Conclusion

The case highlights how a wide differential may have prevented a patient with peripheral neuropathy from developing further sequela of her disease state, by allowing for close monitoring of her bodily function to ensure appropriate treatment if she were to develop plasma cell dyscrasia. As shown by this patient, the rare might not be so rare, but instead hidden in plain sight and through a thorough investigation brought to the light before harms are received by the patient (31).

Deceleration

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Conflict of interest

The authors have no conflicts of interest to disclose.

Consent for publication

This manuscript has been approved for publication by all authors.

Informed consent has been taken from the patient for publication his case.

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