CASE REPORT

Warfarin improves neuropathy in monoclonal gammopathy of undetermined significance

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SUMMARY

We report a case of a 60-year-old man who was referred to a palliative care clinic with monoclonal gammopathy of undetermined significance (MGUS)-associated neuropathy, responding to a therapeutic trial of warfarin. Electromyography showed distal symmetric sensory axonal neuropathy. The patient reported having had improvement of his neuropathic symptoms while taking warfarin postoperatively for thromboprophylaxis 1 year prior, and recurrence of his symptoms after the warfarin was discontinued. The patient was rechallenged with a trial of warfarin, targeting an international normalised ratio of 1.5–2.0. His pain scores decreased from 5/10 to 3/10 at 1 month and symptom improvement was maintained through 24 months of follow-up. Warfarin had a remarkable impact on our patient's symptoms and quality of life. The mechanisms mediating the symptomatic benefit with warfarin are unclear; however, a placebo effect is unlikely. Further studies may help guide the use of warfarin for MGUS-associated neuropathy.

BACKGROUND

Population-based studies estimate the prevalence of monoclonal gammopathy of undetermined significance (MGUS) as being 3.2% in people older than 50 years.¹ MGUS is often underdiagnosed^{2–3} because there are few classic signs or symptoms typically associated with malignant B-cell diseases such as fatigue, bone pain, renal failure, anaemia and hypercalcaemia. Even though most patients with MGUS are clinically asymptomatic, 8–37% may have symptomatic neuropathy.^{4–6}

MGUS is characterised by a proliferation of M-proteins, most commonly IgG, followed by IgM and IgA.⁷ Peripheral neuropathy (PN) is associated with all three, but most commonly seen with IgM-MGUS and least commonly with IgA-MGUS.⁷ IgM antibodies binding to myelin-associated glycoprotein (MAG) are thought to damage interactions between Schwann cells and axons.⁸ The pathophysiology of IgG and IgA MGUS-associated neuropathy is less clear. Glycoproteins other than MAG may also be targeted by antibodies, resulting in progressive immune-mediated inflammation of peripheral nerves. Trials of intravenous immunoglobulin (IVIg), plasmapheresis, immunosuppressants and corticosteroids have produced favourable responses in some patients with MGUS-associated neuropathy.^{9–15}

In this case report, we present a 60-year-old man with an IgA-MGUS-associated distal symmetrical axonal neuropathy experiencing symptomatic benefit from warfarin therapy.

CASE PRESENTATION

A 60-year-old retired skilled professional presented to a neurosurgery clinic, reporting of numbness in his feet for 7 months. Initial involvement of his fourth and fifth left digits had progressed to all toes and the plantar surface of his foot. His right foot then became similarly affected. Lumbar spine MRI showed postsurgical changes at L5-S1 but no evidence of spinal stenosis. MRI results were consistent with a hip replacement and L5-S1 laminectomy performed 10 years prior for left leg pain, which had resolved after surgery. In addition to numbness, the patient reported pain that was exacerbated by walking and interfered with sleep. Neurological examination showed decreased sensation to pain, temperature and light touch on the plantar area of both feet, left greater than right. Vibration sense was 15 s at the ankle and nine at the toe, motor examination was 5/5 throughout, and ankle reflexes were decreased bilaterally. The differential diagnoses included metabolic, infectious, autoimmune and inflammatory aetiologies. Laboratory investigations included complete blood count, comprehensive metabolic profile, erythrocyte sedimentation rate, C reactive protein, serum ferritin, folate, vitamin B12, vitamin B6, copper, antinuclear antibody (ANA), rheumatoid factor, hepatitis panel, paraneoplastic panel, serum protein electrophoresis, urine protein electrophoresis, thyroid stimulating hormone and rapid plasma reagin. The results were unremarkable except for a positive ANA and immunofixation demonstrating an IgA lambda paraprotein. Free κ and λ light chains were within normal limits and cryoglobulins were negative. Cobalt and chromium levels were normal and ruled out a concern for polyneuropathy related to cobalt-chromium metallosis after hip replacement.

Electromyography showed distal symmetric sensory axonal neuropathy with chronic lumbar radiculopathy. Nerve conduction studies were normal except for a decrease in amplitude of bilateral superficial peroneal sensory nerves, and absent bilateral medial and lateral plantar response. Disposable concentric needle examination of the muscles was normal. Positive results on preliminary labs for ANA prompted a work up for inflammatory rheumatological disorders, which was essentially negative. Light chain amyloid-associated neuropathy was suspected and sural nerve biopsy recommended. The patient was reluctant to undergo nerve biopsy, and instead underwent a skin biopsy, which showed normal epidermal nerve fibre density in the left thigh and

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significantly-reduced epidermal nerve fibre density in the left calf, consistent with small fibre neuropathy. Skin biopsy was negative for amyloid by Congo red stain; the patient continued to report of worsening numbness, now involving both hands and with minimal relief from gabapentin 300 mg twice daily. Higher doses of gabapentin did not provide additional relief and the patient was troubled by drowsiness.

After revision of his metal cobalt hip prosthesis, the patient noticed that the hand numbness had disappeared and foot numbness improved significantly while on warfarin for postsurgical deep vein thrombosis prophylaxis. The numbness returned a few days after the warfarin was discontinued. Based on his progressive, intractable symptoms, the patient requested resumption of warfarin therapy. Neurological examination was significant for decreased vibration sense of 10 s at the ankles and 8 s at the toe. Given the high risks associated with warfarin, the patient was treated with pentoxifyline, which was soon discontinued due to intolerable side effects. A subsequent trial of cilostazol failed to relieve his symptoms and he was referred to haematology–oncology for further evaluation of IgA λ paraproteinaemia and the possibility of amyloid neuropathy. Bone marrow biopsy and flow cytometry were normal and Congo red stain for amyloid was negative in the core bone marrow biopsy. Doppler ultrasound of bilateral lower extremities was normal and ruled out arteriovenous insufficiency.

OUTCOME AND FOLLOW-UP

After oncology evaluation, the patient was referred to the palliative care clinic, where he reported poor quality of life, unbearable symptoms and inability to participate in outdoor activities with his family. He had been very active prior to the neuropathy and insisted that warfarin ‘made all my symptoms go away’. His Edmonton Symptom Assessment Scale (ESAS) revealed a pain score of 5/10, wellbeing 6/10, sleep 8/10 and depression 1/10 (see figure 1).

After an interdisciplinary evaluation and informed consent, he was started on warfarin 2.5 mg orally with a target international normalised ratio (INR) of 1.5–2.0. One month later, he reported, ‘pain beginning to improve’. ESAS scores improved to 3/10 for pain, 0/10 depression and 0/10 sleep (figure 1). He reported

improvement of neuropathy in the reverse order of its initial progression, and while he still had some discomfort, he was able to stay on his feet for prolonged periods and even participate in dancing for the first time in years. The improvement has been sustained for 24 months and he reports better relief with an INR closer to the upper limit (2.0).

DISCUSSION

Our patient presented with IgA MGUS, which is clinically and physiologically heterogeneous, and has a high tendency for evolution and progression to malignancy.¹⁶ In general, neuropathy due to MGUS is insidious and progresses slowly over months to years. The most common presentation is distal, symmetric, sensorimotor neuropathy with lower extremities affected earlier and to a greater extent than upper extremities. Muscle stretch reflexes are universally decreased and electrodiagnostic studies commonly show evidence of demyelination and axonal degeneration. Progression of neuropathy in MGUS has prognostic implications, since it may signal conversion of the underlying benign disorder into a malignancy.¹⁷ IVIG, plasmapheresis, corticosteroids, immunosuppressants and rituximab have been used in carefully selected patients with MGUS-associated neuropathy, with limited success.^{9–15} Our patient was not considered a candidate for these treatments.

The mechanisms mediating the symptom relief in our patient are unclear. A population-based study reported the relative risk of venous thromboembolism in MGUS as being 3.3 compared with that of the entire population.¹⁸ However, the vascular work up in our patient was negative and his clinical presentation inconsistent with other prothrombotic conditions such as livedoid vasculopathy, where warfarin has been reported to improve neuropathy and skin ulcers. An underlying vasculitis with ischaemia to peripheral nerves also seemed unlikely, given that he had no cryoglobulins on repeated testing and no cutaneous signs of vasculitis.¹⁹ Another possible mechanism may be related to the inhibition of activated vitamin K, even though vitamin K has been associated with widespread physiological benefits,²⁰ including an antinociceptive effect of vitamin K2 in diabetic mice.²¹ However, a study in PCD 12 animal cells showed vitamin K enhanced nerve growth factor-mediated neurite

Figure 1 Edmonton Symptom Assessment Scale (ESAS) before and after Warfarin (4-week interval).

outgrowth.²² Chronic pain and hypersensitivity have been associated with abnormal nerve sprouting, and we can theorise that warfarin may inhibit vitamin K-associated potentiation of neurite outgrowth.²³ NMDA antagonism may be another potential mechanism, since overexpression of the NMDA receptor is associated with neuropathic pain, and warfarin enhances glycine site binding of NMDA receptor antagonists such as 4-hydroxyquinolones.²⁴ However, our patient was not taking any medications that may behave as a NMDA antagonist. Additionally, although animal studies indicated benefit, a multicentre randomised controlled trial of a glycine antagonist in humans showed no improvement for neuropathic pain.²⁵

A comprehensive multidisciplinary assessment ruled out a number of aetiologies for PN in our patient, and a psychological evaluation indicated depression, anxiety and somatisation were unlikely explanations for his pain. Despite medicolegal and ethical concerns about a high-risk, previously unreported therapy, warfarin continues to have a remarkable impact on symptoms and quality of life in our patient with MGUS-associated neuropathy. Our patient continues to report sustained improvement in his symptoms while on warfarin. Symptomatic improvement was mostly noted when the INR was maintained around 2.0. The mechanisms mediating symptom relief with warfarin are unclear, although a placebo effect seems very unlikely given our patient's history. Further studies to help guide the use of warfarin for MGUS-associated neuropathy may be a challenge given the medication's high risk for adverse effects; however, patients with MGUS-associated neuropathy on warfarin therapy for other conditions requiring anticoagulation, should be observed for symptom benefit, potentially guiding future research.

Learning points

- ▶ This is a case of a 60-year-old man with an IgA-monoclonal gammopathy of undetermined significance (MGUS)-associated distal symmetrical axonal neuropathy who experienced symptomatic benefit from warfarin therapy.
- ▶ Warfarin continues to have a remarkable impact on symptoms and quality of life in our patient with MGUS-associated neuropathy.
- ▶ Symptomatic improvement was mostly noted when the international normalised ratio was maintained around 2.0.
- ▶ The mechanisms mediating symptom relief with warfarin are unclear.
- ▶ Patients with MGUS-associated neuropathy on warfarin therapy for other conditions requiring anticoagulation, should be observed for symptom benefit, potentially guiding future research.

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