Dear Sirs,

Anti-myelin-associated glycoprotein (MAG) antibody is the most common IgM paraproteinemic neuropathy, characterized by sensory symptoms, gait ataxia, and slowly progressive course. Cryoglobulins, both type I (monoclonal IgMs or IgGs, rarely IgAs) and type II (mixed forms) may also be associated with IgM paraprotein, both of undetermined significance (MGUS) or B-cell malignancies, with a predominance of type II cryoglobulins in Waldenström's macroglobulinemia. The association of anti-MAG antibody neuropathy and cryoglobulins has rarely been described [12, 14] The COVID-19 pandemic and also vaccination against SARS-COV-2 have raised concerns for the worsening of both immune-mediated neuropathies and cryoglobulinemia. Consistently recommendations have been developed by appropriate task forces both for inflammatory neuropathies [6] and for cryoglobulinemic vasculitis [10]. Subsequently the short-term safety of the vaccines has been reported both in inflammatory neuropathies and in cryoglobulinemias.

Data from a multicenter Italian study observed post-vaccination vasculitis flares in 5.3% of subjects from a cohort of 416 patients with mixed cryoglobulinemic vasculitis [13]. Despite flares were in line with those observed in other autoimmune diseases [16], patients with purpura or neuropathy seemed at greater risk for symptoms’ exacerbation.

We report on a patient with long-lasting paucisymptomatic anti-MAG antibody neuropathy who developed a cryoglobulinemic flare and severe neuropathy worsening after the first dose of the mRNA coronavirus disease 2019 vaccination. Sural nerve biopsy documented the vasculitic process.

Case report

A 87-year-old woman with a 10-year-history of mild sensory demyelinating neuropathy associated with anti-MAG antibody, complained of mild distal paresthesias at feet that did not affect her gait or functionality, INCAT (Inflammatory Neuropathy Cause and Treatment) Disability Score 0.

In her past medical history, she was affected by high blood pressure and heart loss.

In May 2021, she underwent the first dose of the mRNA-1273 coronavirus disease 2019 vaccination with rapid worsening of symptoms and occurrence of motor involvement (lower limbs) that required hospitalization. Purpura also occurred. Shortly she became unable to walk and needed wheelchair to walk outdoor (INCAT lower limbs 4) and had trouble in doing zips and buttons (INCAT upper limbs 2).

Blood test revealed increased IgM levels (2.96 g/L, normal value 0.4–2.38 g/L), two IgM monoclonal gammopathies (total sum 1.37 g/L), cryoglobulins (2%, monoclonal IgM-type) and increased rheumatoid factor (244Ku/L). Antibodies to MAG were positive 51,404 BTU. Complement was consumed (C3 0.94 g/L, normal range 0.9–1.8 g/L; C4 0.06 g/L, normal range 0.09–0.36 g/L).

Levels of anti-MAG antibodies were unchanged after vaccination. On the other hand, cryoglobulinemia was absent before vaccination and present at 2% soon after vaccination.

Neurophysiology revealed a severe mixed (demyelinating and axonal) polyneuropathy at four limbs, worse at lower limbs. Sural nerve biopsy (6 months after the vaccination) showed prominent focal axonal loss with rare residual myelinated fibers and axonal degeneration, perivascular epineurial infiltrates of mononuclear inflammatory cells also the with presence of hemosiderin deposition. The pathological

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picture was consistent with a microvasculitic process (Fig. 1). Some residual fiber showed demyelination. Immunofluorescence was negative for IgM deposition and electron microscopy of rare residual fibers did not show widening of myelin lamellae. The patient was treated with steroids with improvement of the active vasculitic skin lesions, but despite intensive physical therapy her gait remained unstable, and she needed bilateral support (walker) also to walk at home, and wheelchair in outdoor space. The patient, who loves painting as hobby, complained of disabling tremor, that prevented her from painting and was never present in the previous years.

At neurological evaluation 7 months after the flare onset the patient, who was still in low dose oral steroid therapy (prednisone 10 mg/die), was able to walk only a few steps without assistance with an ataxic and bilateral stepping gait. Strength was reduced distally bilaterally, worse on the right side: tibial anterior 3/5 MRC at the right side, 3.5/5 at left side, extensor hallucis longus and extensor digitorum longus 0/5 at right side, 2/5 at left side. Sensory loss and reduced vibration sense were present up to the knees (0/8 allux, 2/8 ankle, 4/8 knee), deep tendon reflexes were absent at lower limbs. Petechial scars were present in the lower limbs. Total INCAT was 5 (upper limbs 2, lower limbs 3). Steroids were discontinued. The patient underwent bone marrow biopsy that revealed a small clone of k-restricted B lymphocytes CD19+CD5+CD11c+ and MYD88 L265P mutation was absent (details on the assessment of MYD88 mutation has been previously reported in [4]. A marginal zone non-Hodgkin lymphoma, which is commonly associated with cryoglobulinemia and sometimes with MAG neuropathy [3] was diagnosed.

She underwent therapy with 4 weekly rituximab 375 mg/m² (from March to April 2022), with prompt benefit. At neurological evaluation at the beginning of April, the patient was able to walk without assistance, although cautiously, she was able to move the fingers of the feet, functionality also improved with decreased need of bilateral support at home. Distal strength had also improved (right anterior tibial 4.5 MRC, left anterior tibial 4.5/5 MRC, right extensor hallucis longus and extensor digitorum longus 2/5 MRC).

After treatment serum IgM decreased to 1.47 g/L, sum of monoclonal gammopathies to 0.7 g/L, rheumatoid factor to 58 Ku/L, antibodies anti-MAG titer to 21180 BTU and cryoglobulins disappeared. Complement level normalized (C3 0.94 g/L and C4 0.18 g/L).

Five months later (September 2022) the patient showed further improvement. Her gait was possible with no support (although the patients uses the walker to walk outdoor for greater safety), strength fully recovered apart from a mild weakness at right tibial anterior (4.5/5 MRC). No sensory loss was present. Vibration was 0/8 at allux, 2/8 ankle, 5/8 knee, 6/8 index bilaterally. Deep tendon reflexes reappeared at knees. Tremor was absent. INCAT of upper

![Fig. 1 Sural nerve biopsy. The nerve fascicles demonstrated multifocal fiber loss (A, B) (toluidine blue). Demyelination in a teased fiber (C). Perivascular inflammatory infiltration in paraffin section (D) (H&E stain), stained with T cell marker (E) (CD45Ro). Bar = 50 μm](image-url)
limbs was 0, for lower limbs it was 3. The patient was able to swim during the summer vacation and is undergoing active physical therapy.

**Discussion**

Relapse of cryoglobulins vasculitis [9, 15] or other autoimmune diseases [7, 11] after SARS-COV-2 vaccines have already been described. Although autoimmune diseases seem more commonly triggered after adenovirus vectored SARS-CoV-2 vaccines [8], also mRNA vaccines, stimulating the immune system, may worsen autoimmune diseases [7, 9, 11, 15]. However mRNA vaccine for SARS-COV-2 is recommended in cryoglobulinemic vasculitis being the benefit/risk in favor of vaccination [10]. Here we report on a patient with long-lasting paucisymptomatic anti-MAG antibody neuropathy who developed a cryoglobulins flare and likely also a worsening of the underlying autoimmune neuropathy with ataxic gait and onset of disabling upper limbs tremor. The patient quickly responded to steroid therapy, with disappearance of the cutaneous manifestations. However, the gait instability (severe ataxic stepping gait) and tremor did not ameliorate after steroids, and were greatly disabling, limiting patient’s daily activities and autonomy.

Rituximab, an anti-CD20 chimeric monoclonal antibody, has been shown to improve cryoglobulins vasculitis [5] and almost half of patients with anti-MAG antibody neuropathy [2].

The findings from sural nerve biopsy confirmed the vasculitic process and did not show IgM deposition or widening of myelin lamellae, characteristics of anti-MAG antibody neuropathy, probably due to the low amount of residual fibers in the sural nerve. Therefore, some of the main pathological characteristics of the anti-MAG neuropathy cannot be found in the sural nerve biopsy, but it was possible to detect the presence of demyelination on the rare teased fibers.

Finally, in the sural nerve of our patient, the pathological picture of marked axonal loss secondary due to cryoglobulinemic vasculitis overwhelmed the possible pre-existing alterations due to anti-MAG neuropathy [1].

In our patient, rituximab, probably due to its efficacy on both cryoglobulinemia and anti-MAG neuropathy, greatly improved the clinical picture of the patient ameliorating both the sensory abnormalities, that were fully regained at lower limbs, and motor weakness. Tremor disappeared allowing the patient to resume painting.

**Author contributions** CB and AV visited and treated the patient and wrote the manuscript, MT e SG performed nerve biopsy and revised the manuscript, LT revised the manuscript and proved intellectual inputs.

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**Data availability** Data are available upon motivated request.

**Declarations**

**Conflicts of interest** The authors have no clinic of interest with this report. CB is member of the European Reference Network for Neuromuscular Diseases.

**Ethical approval** Not applicable.

**Informed consent** The patients signed informed consent to publish in anonymous way her story.

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