


Polyneuropathy: A Rare and Challenging Presentation of Essential Mixed Cryoglobulinemia

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Abstract

A 49-year-old male presented with acute chronic sensory motor bilateral lower extremity polyneuropathy. Electromyography showed bilateral acute sensory motor axonal polyneuropathy. Lumbar spine magnetic resonance imaging showed diffuse bone marrow replacement and bilateral ankylosing spondylitis. Laboratory workup revealed elevated inflammatory markers and low G6PD (glucose-6-phosphate dehydrogenase) level. Due to elevated acute phase reactants, inflammatory polyneuropathy was suspected; patient was treated accordingly with resolution of neuropathy. Three months later, he relapsed and presented with disabling polyneuropathy and renal impairment, which prompted renal biopsy. Renal histopathology revealed the, otherwise mysterious, etiology, essential mixed cryoglobulinemia. Essential mixed cryoglobulinemia was not considered initially due to the absence of classic systemic manifestations of autoimmune disorders.

Keywords

cryoglobulinemia, peripheral neuropathy, ankylosing spondylitis, bone marrow replacement, glucose-6-phosphate dehydrogenase

Introduction

Essential mixed cryoglobulinemia (EMC) is a vasculitides syndrome caused by circulating cryoglobulins that contain polyclonal IgG (immunoglobulin G) and IgM in the absence of an underlying disease that often involves a coalescence of symptoms.¹ Polyneuropathy is quite common in patients with EMC, but the low prevalence of systemic vasculitides makes EMC one of the rarest polyneuropathy etiologies, let alone being an isolated or a presenting symptom. If that is the case, the diagnosis of cryoglobulinemic-polyneuropathy would then be even more challenging.

Case Presentation

A 49-year-old African American male with past medical history of hypertension, hemosiderosis, and arthritis presented with progressive burning and tingling in his hamstrings and feet bilaterally (right > left) for 2 to 3 years that significantly worsened for 3 to 4 weeks prior to admission. Burning sensation involved most of the left foot and the dorsal aspect of the right. He reported low back pain and weakness around the quadriceps and calf muscles that worsens toward night. No changes in urinary or bowel habits; no thoracic or cervical back pain, headaches, fevers, chills, or sweating. No changes in speech, vision, or swallowing. No

dizziness, lightheadedness, nausea, vomiting, or diarrhea. He does not participate in outdoor activities, does not recall any tick bites, and did not travel recently. He has worked as an operator in an aluminum factory for several years. He is not on any medications at home. He is a former smoker (18 packs/year; quit 5 years ago), drinks 5 to 6 cans of beers and 1 to 2 shots of liquor/week, and does not use illicit drugs. He was prescribed pregabalin and oral prednisone (40 mg/day for 7 days) by his primary physician, but no improvement was achieved.

On examination, he was hemodynamically stable, body mass index of 28 kg/m². On neurologic examination, he was alert and oriented with fluent speech and intact cranial nerves II to XII and coordination. Muscle strength was

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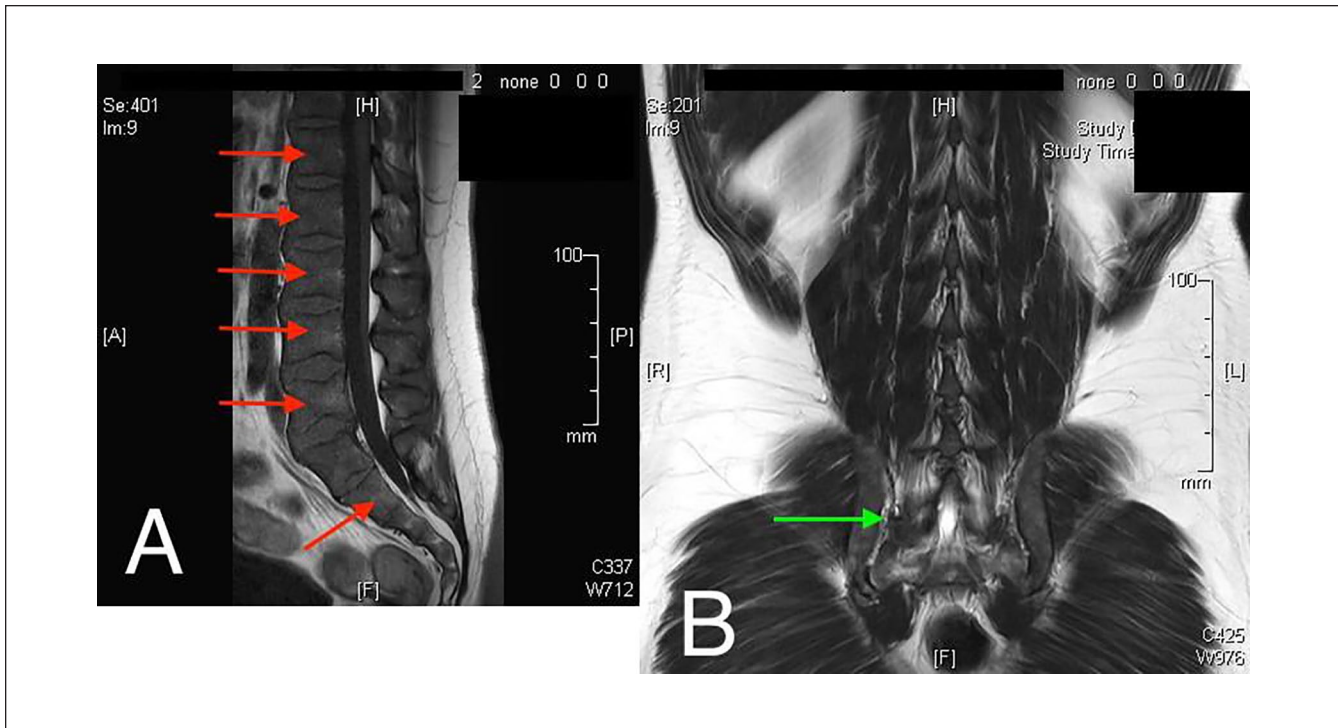


Figure 1. Lumbar spine magnetic resonance imaging. (A) A sagittal T1 sequence shows diffuse hypointense signal of the lumbo-sacral spine (red arrows). (B) An axial T2W sequence showing bilateral sacroiliitis (right > left; green arrow).

decreased in the distal lower extremities, patellar, and Achilles deep tendon reflexes were 2+, toes were down-going, and no ankle clonus was present. Sensation to touch was impaired bilaterally on the feet and distal lower extremities, left greater than right. Distal pulses were palpable and systemic examination was otherwise unremarkable. Laboratory tests showed normal complete blood count and complete metabolic panel (serum creatinine 1.0 mg/dL and glomerular filtration rate 90 mL/min), C-reactive protein = 10 mg/L, erythrocyte sedimentation rate = 106 mm/h, ferritin = 1286 ng/mL, rheumatoid factor = 31 IU/mL, (+) anti Ro, (+) anti-La, (+) anti-nuclear antibodies = 1:1280, elevated SSA and SSB, glucose-6-phosphate dehydrogenase (G6PD) level = 6.6 U/g. An extensive rheumatological workup was also done, all results were normal (Supplementary File 1, available online).

Lumbar spine magnetic resonance imaging showed abnormal, diffuse, hypointense bone marrow signaling, and diffuse ankylosis of sacroiliac joints (right > left; Figure 1). Due to magnetic resonance imaging appearance, bone marrow biopsy was done, showing adequate cellularity with active maturing trilineage hematopoiesis and 2% plasma cells with no significant pathologic abnormality noted. Serum protein electrophoresis was negative for monoclonal gammopathy. Flow cytometry and cytogenetics analysis were normal. Cerebrospinal fluid analysis demonstrated normal cell counts, chemistry, and cytology; it was also negative for acid-fast bacilli, Lyme, West Nile, cryptococcal, and

cytomegalovirus titers and showed normal IgG (immunoglobulin G) and myoglobin index; no oligoclonal bands.

Electromyography (EMG) demonstrated left sural and superficial peroneal sensory nerves low amplitude on left side and absent on right. Right common peroneal and left tibial motor nerves showed absent conduction while left common peroneal motor and right tibial motor nerves showed mild slowing velocity. Normal needle EMG examination at L₁-S₁. Based on EMG results and the acuity of symptoms, a sensorimotor axonal peripheral neuropathy was thought to be inflammatory, and the patient was treated with 5 days of intravenous immunoglobulin (IVIg).

Patient exhibited significant neurological improvement and was discharged to closely follow-up in clinic. Unfortunately, patient lost follow-up due to COVID-19 (coronavirus disease 2019) pandemic and presented to the emergency department after 3 months with bilateral lower extremity disabling neuropathy. Neuropathic pain became severe enough to restrict his ability to perform daily activities. Based on the previous EMG findings and the persistence of symptoms for >8 weeks, a presumptive diagnosis of sensory-predominant chronic inflammatory demyelinating polyneuropathy was made, and the patient received another 5-day round of IVIg; unfortunately, no clinical improvement was achieved.

On second admission, kidney function noticeably deteriorated; serum creatinine was 2.9 mg/dL (up from 1.0 mg/dL) and glomerular filtration rate was 24 mL/min (down from 90

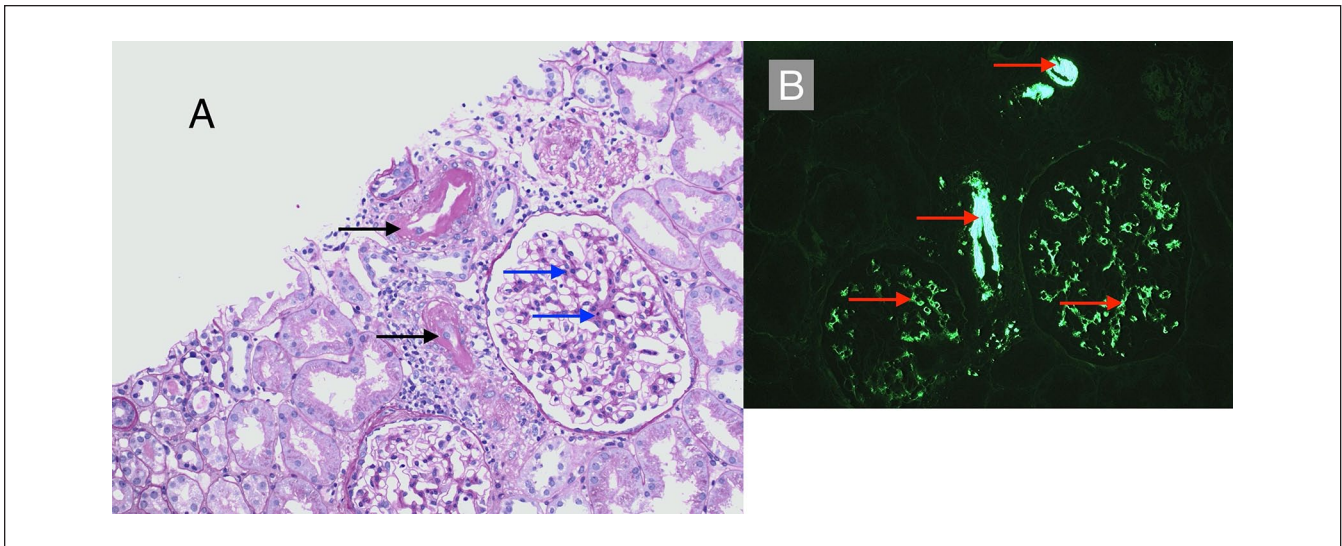


Figure 2. Histopathology and immunofluorescence of kidney biopsy. (A) Renal biopsy periodic acid-Schiff (PAS) stain, 100× magnification, showing multifocal endarteritis (black arrows) and mesangio-proliferative glomerulonephritis (Blue arrows). (B) Immunofluorescence showing arteriolar and glomerular IgM-kappa dominant deposits (Red arrows) consistent with cryoglobulinemic vasculitis and glomerulonephritis.

mL/min). Patient denied any cause of volume depletion or nonsteroidal anti-inflammatory drugs use. Urinalysis was normal with no casts. Renal ultrasound showed normal kidney size and echotexture, no hydronephrosis or hydronephrosis. Acute onset of renal failure which was otherwise unexplainable prompted kidney biopsy, which showed multifocal endarteritis with mild mesangial proliferative glomerulonephritis and IgM-kappa dominant deposits diagnostic of cryoglobulinemic vasculitis and glomerulonephritis (Figure 2). Serum cryoglobulins analysis revealed type II mixed cryoglobulinemia. Hepatitis panel negative, C3 normal but C4 low, leading to the diagnosis of EMC. Afterward, the patient completed 5 days of total plasma exchange, received pulse-dose steroid therapy, and was started on rituximab. He was then discharged on a maintenance dose of oral steroids.

Discussion

The incidence of EMC as an etiology for polyneuropathy has not been widely reported, primarily because of disease rarity (~1/100000). Small studies sporadically reported the prevalence of polyneuropathy among EMC patients; Ferri² (100 patient cohort) showed that 91% of EMC patients had neurological complaints, with 67% of them had abnormal EMG findings too. Ammendola and colleagues,³ another small prospective cohort, showed that polyneuropathy was detected in 90% of EMC patients. Despite polyneuropathy being quite prevalent in EMC, the low prevalence of systemic vasculitides makes EMC one of the rarest polyneuropathy etiologies.⁴

When it affects peripheral nerves, EMC leads to neuronal ischemia primarily by immune-complex-mediated epineurial vasculitis.⁵ Peripheral nerves eventually display axonal

degeneration due to degeneration of the vasa vasorum.⁶ Although the histological demonstration of cryoglobulins would provide the definitive diagnosis of EMC-related polyneuropathy, nerve biopsy is rarely sought in clinical practice. It is primarily because the diagnosis can be achieved with an alternative method, either serologically or by biopsying another organ, and EMC-related neuronal damage would then presumed within the clinical context.⁷ In our case, the diagnosis was established by performing a kidney biopsy.

In this patient, the distribution and nature of neurological symptoms were most characteristic of a neuropathic process. The timeframe of the symptoms and the previously normal EMG argued against axonal neuropathy classically caused by systemic diseases such as diabetes mellitus or vitamin B₁₂ deficiency. Furthermore, the presence of normal reflexes was inconsistent with inflammatory polyneuropathies like Guillain-Barré syndrome. Although our patient had mild multisystemic complaints for several years, his primary presenting complaints were neuropathic. Only a review of previous laboratory findings alluded to his neuropathic symptoms potentially being inflammatory, but none of the abnormal test results clarified the true nature of that inflammatory abnormality in isolation. The kidney biopsy alone provided more certainty.

EMC is an inflammatory process; therefore, it may often be associated with acute phase reactants, potentially explaining abnormal laboratory test values without clear additional rheumatologic or auto-immune clinical manifestations.⁸ This may clarify the abnormal inflammatory laboratory findings in our patient, such as elevated ANA, SSA, La, Ro, and RF titers. However, in our case, several other conditions were present that were not reported to be associated with EMC in

current literature. Those include bone marrow replacement process and ankylosing spondylitis (Figure 1) as well as low G6PD levels.

In a nutshell, though neuropathic symptoms are commonly associated with cryoglobulinemia, it is unusual that they would be the presenting complaint. In the context of abnormal, yet nonspecific, inflammatory markers and the rapid development of neurological symptoms, cryoglobulinemia should be considered even in the absence of other classic symptoms such as purpura or renal insufficiency. It remains unclear whether the findings of low G6PD levels, ankylosing spondylitis, and bone marrow replacement were related to EMC or were incidental bystanders. Further studies are needed to explore this relationship.

Highlights and Learning Objectives

- This report reminds physicians about the difficulty of correctly diagnosing cryoglobulinemia if polyneuropathy is the sole presenting symptom.
- Essential mixed cryoglobulinemia can be associated with ankylosing spondylitis, bone marrow replacement, and low glucose-6-phosphate dehydrogenase levels.

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Ethics Approval


Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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Supplemental Material

Supplemental material for this article is available online.

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