RRNMF Neuromuscular Journal

vol. 6:2 August 2025

The Official Journal of:

EDITORS

Cover image: *The Harvesters* by Pieter Bruegel the Elder, oil on wood, 1565. On view at The Metropolitan Museum of Art, New York. Public domain.

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Letter from the Founding Facilitator for Volume 6, Issue 2

Richard J. Barohn, MD

This issue of the journal begins again with editorials from two of our frequent contributors, Josh Freeman and Don Frey, both former chairs of family medicine (Josh at University of Kansas Medical Center and Don at Creighton University School of Medicine). Another editorial is from a patient with ALS, Elizabeth Greenstein, and her son, Ethan (her caregiver), who comment on an earlier publication by Dr. Richard Bedlack on the challenges of FDA approval for new drugs for ALS. The Greensteins agree with Dr. Bedlack and implore healthcare policy makers to reduce the barriers that exist.

The University of Kansas Medical Center neuromuscular group has two reports. One is a report of two cases of neuropathy due to nitrous oxide. The other is an interesting report of a challenging case of neuropathy in the context of the POEMS syndrome.

A case report from neurologists in Columbia, Missouri and Salt Lake City, Utah report a patient with myasthenia gravis who received eculizumab and then developed hemophagocytic lymphohistiocytosis and raises the question: is there is a relationship? Dr. Michael Abraham, a neurologist at the University of Kansas Medical Center, once again graces the journal with one of his exquisite poems.

We are saddened by the passing of three giants in neuromuscular disease. Dr. Julaine Florence, a leader in developing and performing clinical trials in Duchenne muscular dystrophy and who had a long career at Washington University medical school died too young. Dr. John Kissel and I have written some comments on her career and impact in this issue along with her obituary. Dr. Robert Daroff, a world renowned neuropathologist and myasthenia gravis expert, spent most of his distinguished career in Cleveland at Case Western Reserve. He served many years as chair of the neurology department and also served as the editor of Neurology for many years. I still recall the trepidation I had when I sent my early manuscripts to Neurology because they would be returned with his many editorial comments and corrections in RED pencil. I enjoyed interacting with Dr. Daroff at the Myasthenia Gravis Foundation of America meetings over many years. With his many years in health care leadership positions, I also always could look to him to give sound advice and feedback on difficult issues. His obituary was recently published in both Neurology and Annals of Neurology (1) (2). Dr. Peter James Dyck spent all of his career at the Mayo Clinic, Rochester Minnesota. At Mayo, he essentially developed the academic field of peripheral neuropathy. The author of the major textbook, called Peripheral Neuropathy, and hundreds of scholarly papers, many of which have been pivotal in our current understanding of peripheral nerves and nerve pathology, his impact has been enormous. He began a peripheral nerve fellowship at Mayo and trained scores of neurologist who themselves became leaders in the field. Because of both his scholarly productivity and his role as a mentor to many, Dr. Dyck had an enormous impact in the field of neuromuscular disease. The body of work of these three giants will have a lasting legacy that will continue to influence future generations.

The cover art for this issue is by the great Pieter Bruegel the Elder. The painting, from 1565, is called "The Harvesters" and it portrays life in the fields in the July to August time period in the Netherlands. Bruegel painted a six-part series depicting different times of the year. "The Harvesters" shows workers during a hot day doing a number of things: some working, or eating, or laying down. A great summer painting. It seemed appropriate for our summer August issue. The painting hangs in the Metropolitan Museum of Art in New York City and is a public domain image free to the public.

The next issue of this journal will contain, among other items, the abstracts and program for the annual Neuromuscular Study Group meeting. This is the official journal for the NMSG. This year's meeting is Sept. 26 to 28 and once again it is in Stresa, Italy on beautiful Lake Maggiore. More information about the September meeting is at the end of this issue.

Rick

References

1. DeGeorgia M, Leigh R, Sila C. Robert B. Daroff, MD (1936–2025). Neurology. 2025; 105 (1): doi: 10.1212/WNL.0000000000213816.
2. Leigh, R.J., Ruff, R.L. and Devereaux, M. (2025), In Memoriam: Robert B. Daroff, MD (8/3/1936–1/12/2025). Ann Neurol, 97: 807-808. https://doi.org/10.1002/ana.27232

"It was the best of times, it was the worst of times": Threats to the public's health from Medicaid cuts, MAHA, and others

Joshua Freeman, MD

This article orginally appeared in Dr. Freeman's blog, "Medicine and Social Justice." https://medicinesocialjustice.blogspot.com/

"It was the best of times, it was the worst of times..." begins Dickens' "A Tale of Two Cities", and people have used that phrase to describe all kinds of times in the 150+ years since it was published in 1859. But maybe not today. In some ways, I guess, it could be the best of times for some privileged people in wealthy countries; never in history have so many people been able to enjoy things like enough food to eat, shelter, air that is breathable, water that is clean, heat in the winter, A/C in the summer, travel for long distances by plane, for many distances by private car, etc., etc. In every way, often ones that seem to us to be mundane, a lot of us enjoy a standard of living that could not be imagined even by the wealthy of Dickens' time or earlier. Of course, that is only for some of us in the world, it is likely the majority in wealthy countries, even those working people living paycheck to paycheck.

But even in those wealthy countries we see too many who do not enjoy those benefits, who are living on the streets, who sleep in shelters or sewer grates or parks, who are freezing in winter and roasting in summer, who do not have enough to eat, who cannot get basic health care for their needs, and often have additional needs related to mental health or alcohol or drug use. We see children being abused and neglected by parents who do not have the wherewithal or support they need. We are, some of us, outraged and angry, some of us at them, and others of us at the system in which they live. Because we have a society that actively chooses to make the lives of many people worse so that the most privileged can have more.

And, once we leave wealthy countries such as the US, it becomes phenomenally worse. The number of people starving or suffering in wars and armed conflicts is incredible. Gaza is one obvious example, and it is horrific – the government of Israel using the all too real fact of centuries of oppression and anti-Semitism to destroy another people, the Palestinians, killing tens of thousands, displacing millions from their homes, destroying what infrastructure they had stingily allowed to be built – this is not wrongly called genocide. And there is Somalia and South Sudan and Ukraine in wars, and whole continents of people whose best days are the ones on which they get something to eat.

So, is it the worst of times? The policies being followed by the US government under President Trump and the bootlicking GOP Congress and the Supreme Court to which he appointed a disproportionate number of members, are leading us steadily downhill in virtually every part of the public arena. But the fact that they keep getting worse indicates that we have not yet reached bottom, we are not yet in the Europe of the late 1930s and 1940s even. But it does keep getting worse, in the US and across the world. It hits on so many fronts – the economy, basic human rights, climate, war – that it is difficult to even keep up.

And health and health care? The focus of this blog? Still lots of bad things, starting with the cynical, opportunistic, and dangerous policies being implemented by the Secretary of Health and Human Services (HHS), Robert F. Kennedy, Jr., the director of the Centers for Medicare and Medicaid Services (CMS), Dr. Mehmet Oz, and others in the administration, which become more and more outrageous. And, of course, the negative impact of the President's "Big, Beautiful Bill" on those dependent on Medicare and Medicaid will be dramatic. STAT News recently reported that the Congressional Budget Office (CBO) estimates 11 million people will lose their health coverage as a result of Medicaid cuts. That is a lot of people, and only a very tiny percentage are the "boogeymen" cited by the GOP as deadbeats, adults capable of working but not seeking work. In fact, most people on Medicaid are children and their mothers, and most Medicaid dollars are spent on caring for seniors and disabled people in long-term care, and most able-bodied adults receiving Medicaid are already working, sometimes at more than one job, but making less than the standard (often 138% of the Federal Poverty Level). In my state, Arizona, that is less than $22,000 a year for a single person, and it is similar for families and in other states. The outrage is not that there are people receiving Medicaid who should be able to work, but rather that people working full-time can be paid so little that they qualify for Medicaid and other federal benefits. Many of these folks are working for high-profile (and high-profit!) corporations such as Walmart and McDonald's, as reported by CNBC in 2020 (and probably is worse now!) Medicaid, by the way, is not a benefit paid to individuals (such as welfare or SNAP) but rather is paid to medical facilities for providing care to eligible individuals. To the extent that there is fraud, it is more likely to be on the part of those providers than the individuals. And cutting Medicaid threatens the continued existence of many of those providers, particularly rural hospitals which are, because the population that they serve has a higher percent of poor, disabled, and elderly people, more dependent upon Medicaid payments.

Medicare is also being harmed, in less obvious ways than the cuts to Medicaid, largely by encouraging the movement of Medicare recipients into private, insurance

company-run plans called Medicare Advantage. I have often discussed the details (e.g., Open Enrollment Season for Medicare and Medicare Advantage: What you should know, Oct 7, 2024) but, in brief, insurance companies get paid more than Medicare spends on "traditional Medicare" (TM) recipients, and use some of it to provide benefits that are attractive, especially if you are not really sick. Of course, it is not then Medicare, but an insurance package, a PPO or HMO paid for with Medicare dollars, and the insurance company can (and often does) deny claims, as they do for their non-Medicare insurance packages, which TM does not.

And what about RFK, Jr., and his MAHA ("Make America Healthy Again") campaign, including his disparagement of vaccines and advocacy for unproven (and sometimes proven-to-be-dangerous) treatments such as unregulated use of stem cells, and other "alternative" treatments, including saying "'Charlatans' Are No Reason to Block Unproven Stem Cell Treatments" even though "some methods have resulted in blindness, tumors and other injuries"? I'd say there is great cause for concern, but would also recommend reading the sympathetic and balanced discussion of MAHA supporters by Katelyn Jetelina, "Your Local Epidemiologist". She distinguishes between leaders of the movement, like RFK, Jr., about whom she says "I don't believe RFK Jr. is acting in good faith. His record is riddled with contradictions and falsehoods. His tactics often erode trust under the guise of restoring it. Treating him as a serious partner would be a mistake," and the grass-roots. Many of these people feel that they are not getting accurate information (often they are not), many (appropriately) distrust Big Pharma and associate the mainstream medical and public health disciplines with it, and some are advocates for the magic benefits of "alternative" treatments such as stem cells. But a big issue that she identifies is their desire for "autonomy", to make their own decisions on health care (where to go and what to do, what treatments to use, etc.) rather than be forced into using vaccines, or taking pharmaceuticals when they don't want to. This is a big issue. In many areas, particularly infectious disease, individual autonomy that says "we don't want vaccines" can lead to big disease outbreaks (like the ones we've recently seen of measles, which include deaths of unvaccinated children). The issue of individual autonomy vs. the public good is a longstanding tension, and of particular potency in the US.

So, what is there to say? I say do get vaccinated. Vaccines do not cause autism. Childhood vaccines, as is often stated, cause adulthood – because children do not die of polio, measles, or influenza, or epiglottitis and meningitis from H. influenza B, and hepatitis, and all the other conditions which at best cause significant suffering even when they do not lead to permanent disability or death. Vaccines are a good thing.

Swimming in polluted water, as RFK, Jr., has done is a bad idea. Taking your grandchildren along with you, as he has also done, is a really bad idea.

And yes, cutting millions of people, most of whom are hard-working, off of Medicaid, is another really bad idea.

A Lottery Ticket

Donald Frey, MD

This article originally appeared in Dr. Frey's blog,
A Family Doctor Looks At The World.
https://afamilydoctorlooksattheworld.com/

OK, I admit it. I sometimes play the lottery. Just a dollar here and there; after a tank of gas. Why do I waste my time? I'm never going to win. Every bit of my luck was used up 69 years ago when I hit a jackpot that somehow managed to keep me alive.

My mother would sometimes talk about my first birthday, January 7th, 1953. She kept a picture of that day and stares at it from time to time. I still have it. There I am, standing beside a single-candled birthday cake, mouth wide open, looking straight at the camera in either fear or confusion. And I remember how my mother used to gaze at that picture with a faraway look in her eyes and say, "I knew there was something about you that just didn't seem right."

The ensuing spring brought a flurry of respiratory infections I could never quite shake. Finally, in mid-summer, my temperature shot up. In medical lingo I would one day learn, I 'spiked a fever.'

Dr. Lewis Calvert was an institution around Weston. A local farm boy, he received his medical degree from Thomas Jefferson University in Philadelphia then left to become a field surgeon in World War I. Upon returning, he established a practice on Main Street that lasted over 4 decades. He delivered babies until 1952, when the last child he brought into the world was at Cushing Memorial Hospital in Leavenworth—a 7-pound 7-ounce boy named Donald Frey.

He was there for everyone, it seemed, even visiting my grandfather on his death bed at the family farm north of town.

But Dr. Calvert always seemed to have a special fondness for me, and I can't help but wonder if it was because of what happened that summer of 1953. Three years later, I would be one of the first children in Weston to whom he gave the polio vaccine. Maybe he, too, understood that my luck had already run out, and that I needed all the help I could get.

At his office that summer morning, Dr. Calvert examined me and determined that I needed antibiotics. At that time, a physician could count all the different antibiotics in the world on one hand. And of them all, penicillin was the mainstay. He gave me a penicillin injection, the strongest dose he felt he could safely use. Reassured, my mother took me home. I, of course, can remember none of this. Perhaps it's for the best.

Soon, my temperature was spiking again, even more rapidly. My mother called and described my condition. Dr. Calvert explained that he'd given the maximum dosage of penicillin and could do nothing else. My mother sat up with me that night. Later, she would recall the exact chair she sat in, as well as the book she read to keep her mind occupied. But every hour she'd take my temperature. It just kept climbing.

My mother's upbringing was marked by the hard work, resilience, and stoicism that were the hallmarks of early twentieth century Weston. She had ridden a horse 5 miles into town to go to High School, trotting down a dirt road with her neighbor Mary Ruth Richardson Bradley, both dressed in overhauls, their obligatory school dresses stuffed in their saddlebags to be donned when they arrived for class. She had survived the Dust Bowl, when a black sky meant dirt was coming down from the Dakotas, and a red sky meant dust from Oklahoma. She had seen farm foreclosures, savings wiped out, hunger that no one today can even imagine, and neighbors on the brink of collapse. So when my temperature continued to rise, and knowing that no other medical options were available, she responded the only way she knew. When the fever hit 105, she simply stopped taking it.

A short time later, my father came home from the night shift as the agent at the Burlington Depot at the foot of Main Street. Dr. Calvert's office would be opening soon, and it was agreed my father would take me.

Dr. Calvert's office was on the east side of downtown, halfway between City Hall and the Post Office. Such references are meaningless now. Both moved long ago. But I can still remember his office from visits I later made in grade school. It had a simple waiting room and one exam room. His sole staff member was his receptionist, Miss Marie Ohlhausen. She would later become the local librarian, and distribute thousands of books to kids like me.

I've sometimes wondered what I must have looked like, a one-and-a-half-year-old, listless and moaning from fever, lying on my back on Dr. Calvert's only exam table. My mother, always the master of understatement, would recall "you sure didn't look very good." My father was blunter: "You looked like hell."

My Father remembered Dr. Calvert examining me, listening to my heart, my chest, looking in my throat—all the standard elements of a medical exam. Then he paused as if deep in thought, trying to put it all together. At that moment, according to my father, I reached back with my hand, and started rubbing my neck. Dr. Calvert gasped and looked thunderstruck. He placed his hand under the back of my head, and raised my back up off the table. My neck didn't bend. It was stiff as a board. Whatever Dr. Calvert said next, my father remembered only one thing. "We've got to get this boy down to KU right away."

Of course, no ambulances were available at that time, and even if they had been, Dr. Calvert was in no mood to wait. Instead, he and my father, carrying me in his arms, piled into Dr. Calvert's car for a mad dash to the Kansas

University Medical Center. Interstate 29 was still years away. Instead, the route must have been down highway 45, past Beverly and Farley, slipping through Parkville, across the Fairfax Bridge, onto Rainbow Boulevard and KU. Later that day, my mother arrived.

25 years later, as a medical student, I would study the nuances of a disease called cerebrospinal meningitis. Bacteria from a source elsewhere in the body, such as the respiratory infection I was almost certainly carrying, enter the lining of the brain and spinal cord. There, cut off from much of the rest of the circulation, they begin to multiply rapidly. Without immediate treatment, the outcome is disastrous. As we drove toward Kansas City, the growing infection was beginning to gobble up every molecule of oxygen and glucose it could find, each passing moment increasing the risk of a convulsion.

The team at KU followed standard procedure. A spinal tap was performed, and the fluid analyzed. Today, intravenous antibiotics would be started. But this was 1953, and intravenous lines in children were poorly developed. Instead, the Doctors gave the antibiotics through the same needle that was used for the spinal tap, injecting the medication directly into the fluid surrounding my spine and brain. They would continue to do this every six hours for the next ten days.

Every six hours. Ten days. Forty spinal taps. "Your back looked like a little pincushion," my mother would recall.

The specific bacterium found in my spinal fluid was called streptococcus pneumoniae, a highly inflammatory organism infamous for producing pus and swelling around the brain. By the time I got to KU, the pressure inside my skull must have been increasing rapidly.

The textbooks that I would later study were clear in their sober assessment of the disease. Even with the antibiotics of today, the mortality rate for pneumococcal meningitis can be 30%. The complication rate due to scaring of the brain tissue—blindness, deafness, difficulty walking, seizures, and especially brain damage—exceeds 90%. Even with treatment.

Yet somehow, I won the lottery. The child in the crib next to mine received the same treatment prescribed to me. He also survived, but became totally deaf. Not once did anyone observe me having a seizure. When I was brought back to KU for a check-up a month after dismissal, the doctor picked me up off the exam table and stood me on the floor to see if I could walk. Instead, I started to run. I was nearly out of the building before they caught me.

As years passed, I had what most would consider a normal Weston childhood. I could cut a thousand sticks of tobacco in a day, or haul a thousand bales of hay. At one time or another, I probably mowed half the lawns in town. I played football (not particularly well) and was conference champion in the 100-yard dash.

The experience at KU left its mark on my parents, too, and explained some of their odd "rules" that made no sense to me. As a kid, I was never allowed to ride in the back of a pick-up truck like my friends, laughing and bouncing along in the summer breeze. Instead, my father would nearly fly into a rage whenever I'd bring it up.

It wasn't until years later that I learned that one of the other patients on the same ward at KU was a boy who'd been riding in the back of a pick-up driven by his father. They'd hit a bump, and the child was thrown out. He'd landed on his head on the concrete. There was nothing the family could do but wait for hours at the bedside while he died. My father, of course, had watched in silence as it all unfolded.

Physically, I had turned out fine. But as I pondered my medical textbooks, perhaps the most chilling fact I encountered was the near certainty of brain damage in survivors of pneumococcal meningitis. How had I dodged the bullet? It wasn't because of anything I did. It's all lost in that vacuum of events that occur before we're old enough to form memories.

Later, I graduated from medical school, and eventually became responsible for the education of hundreds of students in nursing, pharmacy, medicine, dentistry, and physical and occupational therapy. I published articles, gave lectures around the world, and treated thousands of patients. Some of them were also children with meningitis.

I sometimes talk with medical students about my own history of meningitis. How I survived in an era of minimal treatment. Occasionally, a student will ask if I wound up with any brain damage. I usually shrug, chuckle, and say: "Who knows? Maybe I would have won a Nobel Prize by now if it hadn't been for that damned meningitis." This usually brings about nervous laughter, and the subject quickly changes.

No, the fact is, I had no brain damage. I had no physical problems, either, from the infection, swelling, and inflammation that pummeled my brain and nervous system 69 years ago. In 1953, I somehow squeezed a lifetime of good fortune out of a single event. I've exhausted my luck forever.

I have no idea how much longer I can keep this up. They're all out there. Cancer, heart attacks, strokes, viral pandemics, plane crashes, terrorist attacks. When it happens to me, it happens, I guess. Every one of the past 69 years has just been icing on the cake.

So yes, I sometimes play the lottery. And each time I do, the lady behind the counter hands me the ticket and wishes me luck.

I just smile back at her and say thank you.

Living on the front lines: A demand for faster ALS treatment access

Elizabeth A. Greenstein, Ethan R. Greenstein

Dear Editor,

My name is Elizabeth Greenstein. I have been battling bulbar-onset amyotrophic lateral sclerosis (ALS) since June 2023. I am writing alongside my son, Ethan Greenstein, who is a caregiver of mine and an ALS advocate.

We write to express a deep appreciation for the recent article in *RRNMF Neuromuscular Journal* by Dr. Richard Bedlack and colleagues, titled "A worsening problem in ALS: insurance barriers between drug approvals and patient access." The barriers facing ALS patients in accessing treatments, as outlined in the article, are stark, unjust, and deserve far more of a spotlight than they are currently given.

Part of the reason these barriers receive so little attention is that people with ALS are diagnosed, become very sick, and die within a short period of time. I write to bring this issue to light in a permanent form—while I will not be here forever, I will do everything I can to push for an end to this horrific disease. In the meantime, the least we can do is ensure ALS patients like me have access to the limited treatments that exist.

Since being diagnosed with bulbar-onset ALS, my family and I have been tasked with navigating the complex landscape of healthcare and insurance. The journey has been fraught with obstacles, the most disheartening of which include the insurance barriers that delay access to crucial medications. These delays are detrimental to our health, as the rapid progression of this fatal disease does not allow for the luxury of time.

The article rightly points out the incoherence of labeling FDA-approved therapies as "experimental" and the use of clinical trial criteria to restrict access to medication. These practices are a direct affront to the needs of ALS patients. We require these treatments to maintain function and quality of life for as long as possible. And the time that we are given to begin with is not long—the average person with ALS lives just 2-5 years, with an even poorer prognosis for bulbar-onset ALS.

We urge healthcare policymakers, insurance companies, and the ALS community to come together to dismantle these barriers. Change is urgently needed to ensure no patient is left waiting for the treatments they desperately need.

I am not dying from ALS. I am living with it. Insurance systems should support, not stand in the way of, those of us fighting to preserve our lives and independence for as long as we can.

Thank you once again to Dr. Richard Bedlack and his colleagues for highlighting this pressing issue. It is my hope that their work, combined with voices like mine, will catalyze the necessary changes to make ALS care more accessible and effective for all and, eventually, to find a cure for this devastating disease.

With hope,

Elizabeth Greenstein
Ethan Greenstein

Remembering Dr. Julaine Florence, DPT

Richard J. Barohn, MD and
John T. Kissel, MD

We are publishing the obituary of Dr. Julaine Florence. Dr. Florence was a leader in the field of clinical trials in Duchenne muscular dystrophy (DMD). A physical therapist, Dr.Florence and neuromuscular neurologists at Washington University School of Medicine (where she spent her whole career), Ohio State University College of Medicine, University of Rochester, and Vanderbilt University Medical Center were pioneers in studying the natural history of Duchenne muscular dystrophy and developing multi-center clinical trials, using a number of different medications in an attempt to slow down the course of this disease. The four center partnership, known as the CIDD (Collaborative Investigation of Duchenne Dystrophy) group, developed first- of-their-kind protocols for describing the natural history of the disease and then essentially defined the role of "clinical evaluator" in neuromuscular clinical trials. The group then performed cutting edge investigator initiated clinical trials in the disorder. The other senior members of the initial CIDD group were Dr. Jerry Mendell and Wendy King (Ohio); Dr. Robert (Berch) Griggs and Shree Pandya (Rochester); Dr. Gerald Fenichel and Jenny Robinson (Vanderbilt, Tennessee); and at Washington University, Dr. Michael Brooke (and then Dr. Alan Pestronk) and J Phillip Miller. The work of this group paved the way for the explosion of progress in the treatment of DMD now led by industry. Without the two plus decades of work in the 1970s/80s and early 90s, the field would never have progressed to its current stage. Probably the most extraordinary and surprising discovery of Dr. Florence and the CIDD group were the randomized clinical trials demonstrating that prednisone dramatically slowed down the progression of DMD. Since then, every boy with DMD is put on prednisone to keep them walking as long as possible. The work of Dr. Florence and her colleagues also served as a template for the study of other neuromuscular diseases including facioscapulohumeral dystrophy, myotonic dystrophy, spinal muscular atrophy and Charcot-Marie-Tooth disease amont many others. Dr. Florence was also a superb teacher who participated in countless neuromuscular conferences and courses over the years, contributing her knowledge, insights and experience to any discussions related to neuromuscular disorders. The field of neuromuscular disease, and all patients and families who deal with a neuromuscular disorder (and especially DMD), owe a debt gratitude to Dr. Florence and the entire CIDD group. Dr. Florence was a key leader of the CIDD group and those who knew her will remember her and her highly successful career.

Julaine Marie Florence
May 26, 1953 - May 14, 2025

Julaine Marie Florence of Saint Louis, Missouri passed away on May 14, 2025. Born in Minot, North Dakota on May 26, 1953, she was raised in Velva alongside her four siblings in a home filled with love and joy. She graduated from Velva High School in 1971 and went on to earn Bachelor of Science (BS, 1975), Master of Health Science (MHS, 1983), and Doctor of Physical Therapy (DPT, 2002) degrees from Washington University in St. Louis. Dr. Florence was a clinical researcher, with an appointment as Professor of Physical Therapy at Washington University Medical School.

A prolific researcher, Dr. Florence dedicated her career to improving treatments for children with Duchenne muscular dystrophy, a debilitating genetic disorder that causes progressive muscle weakness and degeneration, with impact on quality and span of life. She co-authored 78 publications and her work has been cited by at least 352 researchers, expanding the reach and impact of her contributions to the field. She would refer to herself as a "stubborn Norwegian," but in truth she was an unstoppable trailblazer; she was ambitious, visionary, committed, and steadfast in pursuit of her goals. She was stoic and withstood adversity with dignity.

A talented athlete in her youth, she is proudly remembered by her family for breaking down barriers and joining the Boys' Track and Field team in high school, where she excelled as a distance runner. She later ran marathons and introduced her children to a lifelong love of sports - both as athletes and as spectators. Dr. Florence cheered for her children at their various sporting events with unbridled pride and excitement. She also inspired in them the importance of caring for others and brought them into her meaningful work through participation in the Jerry Lewis MDA Telethon and MDA Summer Camp. Dr. Florence had a beautiful singing voice and her children will always remember her nightly rendition of Edelweiss before they went to sleep. She loved to read and "was funny until the very end."

Dr. Florence is preceded in death by her parents, Dr. Gerald Florence and Geraldine (Heggerston) Florence and by her brother, Dr. Jonathan Florence.

She is survived by her three loving children, Benjamin (Laura) Phillips of New York, NY, Aaron (Lai) Phillips of

Johns Creek, GA, and Hannah (Brian) Dill of Manchester, CT; six grandchildren (Rebecca, Harper, Riley, Lucas, Bodhi, and Jackson); three sisters, Kari Ann (Paul) Dunderland of Bottineau, ND, Mary Lynn (Mark) Berntson of Grand Forks, ND, and Sara Jane Anderson of Beaver Dam, WI; sister-in-law, Kristin Florence (Tom) Bodine of Velva, ND; and former spouse, Dr. Daniel (Linda) Phillips of St. Louis, MO.

A lakeside memorial will be held this summer with her loved ones at Lake Metigoshe in North Dakota, where she loved spending summers with her family.

In lieu of flowers, please consider donating in her memory to the Muscular Dystrophy Association (MDA; www.mda.org), a primary source of funding for neuromuscular disease research, including the very projects aimed at developing treatments for Duchenne muscular dystrophy that Dr. Florence devoted her life to.

Diagnostic Challenges and Key Insights of Nitrous Oxide Neuropathy: A Case Series

Govind S. Mann MBBS, Mustafa Al-Kharsan MD*, Constantine Farmakidis MD, Mazen M. Dimachkie MD, Long Davalos MD, Mamatha Pasnoor MD

Department of Neurology,
University of Kansas Medical Center

*Corresponding author

Abstract

Nitrous oxide (N_2O) is increasingly misused due to its easy availability. Chronic misuse causes irreversible oxidation of cobalamin which results in vitamin B12 deficiency and impaired myelination leading to neurological complications. We present two cases highlighting diagnostic challenges consisting of a 34-year-old male and a 52-year-old, both initially misdiagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP). They were eventually diagnosed as N_2O-induced neuropathy based on lab testing and electrodiagnostic findings. Clinicians should maintain a high suspicion of N_2O misuse in unclear neuropathies. Early recognition with prompt and sustained vitamin B12 supplementation is crucial for preventing irreversible neurological damage and avoiding unnecessary immunotherapy.

Introduction

Nitrous oxide (N_2O), also known as laughing gas, is an anesthetic agent frequently utilized in medical and dental procedures. Recreational use of N_2O has increased, particularly among young adults, due to its short-acting euphoric and dissociative effects. It is most commonly inhaled from whipped cream chargers («whippets»), balloons filled from gas canisters, or directly from medical-grade cylinders, often accessed via online or over-the-counter sources.[1] N_2O misuse is an emerging public health concern, increasingly identified for causing significant neurotoxicity. Chronic exposure to N_2O leads to vitamin B12 deficiency through irreversible oxidation of cobalamin, impairing myelin synthesis and resulting in peripheral neuropathy and myelopathy.[2,3] Despite rising awareness, clinical differentiation of N_2O-induced neuropathy from inflammatory or autoimmune conditions, such as chronic inflammatory demyelinating polyneuropathy (CIDP), remains challenging and often delays accurate diagnosis and effective treatment.[4] While vitamin B12 supplementation remains central to management, variability in neurological recovery highlights ongoing clinical challenges.[5]

We present two illustrative cases highlighting these diagnostic challenges. The first case involves a 34-year-old male initially suspected of CIDP due to sensory and motor deficits, subsequently diagnosed with N_2O-induced neuropathy. The second case involves a 52-year-old female with subacute painless bilateral foot drop who underwent Intravenous Immunoglobulin (IVIG) therapy without improvement before identification of the toxic etiology. Both cases highlight the critical need for timely recognition of N_2O abuse to initiate appropriate treatment and avoid unnecessary interventions.

Case Presentation

Case 1

A 34-year-old male presented with progressive tingling and numbness that started in the feet and ascended to the knees approximately two weeks following a viral illness. Symptoms evolved over several months, resulting in frequent falls and balance impairment, particularly in low-light conditions. He denied upper extremity weakness, dysphagia, or respiratory issues. His medical history was notable for chronic back pain, prior alcohol dependence, and recreational inhalation of nitrous oxide gas for an unknown duration.

On examination, strength was intact except for mild bilateral weakness of the great toe extensors. Vibration sense was absent up to the knees bilaterally, and proprioception was impaired at the toes. Deep tendon reflexes were absent at the knees and ankles but preserved in the upper extremities. Gait was wide-based, with mild difficulty performing tandem and heel walking. Romberg sign was positive.

Previous nerve conduction studies (NCS) and electromyography (EMG) indicated possible demyelinating neuropathy based on prolong latencies and slow conduction velocities. However, this initial external study did not meet formal EAN/PNS electrophysiological criteria for demyelination upon closer review. Two months later repeat testing at our institution confirmed axonal sensory-motor polyneuropathy. Vitamin B12 was markedly reduced (123 pg/mL, normal: 180-950 pg/mL), with elevated methylmalonic acid (1.66 µmol/L, normal: <0.40 µmol/L). X-ray of the cervical spine was performed and that reported mild degenerative changes. Magnetic resonance imaging (MRI) of the lumbar spine showed mild degenerative changes but no significant stenosis or dorsal column signal.

The patient was diagnosed with N_2O-induced neuropathy with vitamin B12 deficiency. Treatment included cessation of N_2O, 1000 mcg of intramuscular vitamin B12 weekly for four weeks, followed by monthly 1000 mcg injections as maintenance, and ongoing physical therapy. During the last follow-up at the end of January

2025, the patient reported reduced tingling sensation with improved vibration, proprioception and balance following continued abstinence from N_2O.

Case 2

A 52-year-old female with a history of hypothyroidism, breast cancer, Sjogren's syndrome, depression, and prolonged laughing gas use abused whippet canisters for months, consuming up to 200-300 canisters per day at some point in 2022. She presented with relatively simultaneous, painless subacute bilateral foot drop. She described numbness on the soles, impaired balance, and difficulty climbing stairs but denied significant foot pain. Her medical history included multiple hospitalizations for toxic encephalopathy, anemia, and leukopenia. The episodes of toxic encephalopathy, including one with visual hallucinations, were presumed to be secondary to nitrous oxide use and responded to cessation of exposure and vitamin B12 supplementation. Initially, she was evaluated by a neurologist outside our hospital, who performed an NCS/EMG, which there was mention of temporal dispersion on bilateral peroneal nerves. This raised the suspicion of CIDP, and she was started on steroids followed by IVIG, which resulted in no clinical improvement. Blood work at the time showed leukopenia. Three days post-IVIG, she developed a rash involving both lower extremities and torso, leading to us for further workup.

Neurological examination revealed severe bilateral weakness in ankle dorsiflexion (Medical Research Council scale 1/5) and complete loss of toe extension. Vibratory sensation was absent at the toes, with reduced proprioception at the great toes. Reflexes were hyperactive at the knees but absent at the ankles. Her gait was wide-based with bilateral steppage pattern and an inability to heel-toe walk.

Repeated EMG/NCS study in our hospital a month later demonstrated length-dependent pure motor axonal neuropathy, suggesting that the abnormal large fiber sensory findings were likely due to dorsal column involvement. MRI of the cervical spine identified severe central canal stenosis at C4-C5 and C5-C6 level with associated increased cord signal. These findings could potentially explain the brisk lower extremity reflexes and features of sensory ataxia, given the normal peripheral sensory nerve conduction studies. However, they are insufficient to fully account for the motor-predominant bilateral foot drop, suggesting a concurrent peripheral process. MRI of the lumbar spine revealed mild degenerative disc disease at L3–L5 with mild spinal and foraminal stenosis, but no significant compressive pathology to explain the bilateral foot drop. Laboratory studies confirmed vitamin B12 deficiency (111 pg/mL, normal 180-950 pg/mL), leukopenia (white blood count: 2.0/ µL, normal: 4.50-11.00 10^3/ µL) and anemia (Hemoglobin: 9.4 g/dL, normal: 12.0-15.0 g/dL), (MCV 92fL, normal 80-100 fL).

Cerebrospinal fluid (CSF) analysis showed mild chronic inflammatory changes (total nucleated cells 10, normal: <5/ µL; lymphocytes predominant, 91%, and total protein 31 mg/dL, normal: 15-45 mg/dL) however, these were considered to be related to recent IVIG treatment. Dermatology considered a possible leukocytoclastic vasculitis, however not confirmed on a biopsy. The rash improved in few days indicating an adverse reaction to IVIG treatment. A nerve and muscle biopsy were also performed and reported mixed axonal and myelin sheath loss without any evidence of inflammation nor signs of vasculitis. Recognition of N_2O-induced neuropathy prompted initiation of 1000 mcg of intramuscular vitamin B12 weekly for four weeks, followed by monthly 1000 mcg injections. Following two-week period of supplementation, mild improvement in balance and ambulation were seen, though severe foot drop persisted, necessitating ongoing physical therapy, orthotic support, and further diagnostic evaluations. Table 1 summarizes and compares key clinical characteristics, diagnostic findings, treatments, and clinical outcomes of the two patients in this case series.

Discussion

This case series demonstrates diagnostic challenges caused due to N_2O-induced neuropathy which is an increasingly prevalent yet often unrecognized clinical entity. Misuse of N_2O often sourced from medical supplies, whipped cream dispensers, or recreational use, disrupts vitamin B12 metabolism. This disruption can lead to severe neurologic deficits resembling inflammatory and autoimmune neuropathies, which frequently leads to delayed or inappropriate treatment.[6,7]

Our two cases presented with the diagnostic complexity associated with N_2O neuropathy. Case 1 was initially misdiagnosed with CIDP, and Case 2 underwent unsuccessful treatment with steroids and IVIG. In both cases, the initial electrodiagnostic studies performed at outside institutions suggested demyelinating features, which on further review did not meet the formal EAN/PNS criteria for demyelinating neuropathy. Therefore, repeat studies were performed at our center, which demonstrated axonal sensorimotor and motor axonal neuropathies, respectively. Both cases presented with progressive motor and sensory deficits with ataxia manifested as impaired coordination and balance, with lab tests showing severely reduced vitamin B12 levels. Coexisting autoimmune conditions such as Sjogren's syndrome, as seen in Case 2, can significantly complicate the diagnostic landscape. Sjogren's is associated with a spectrum of neuropathies, most commonly presenting as distal symmetric sensory neuropathy, painful small fiber neuropathy, or sensory ganglionopathy. Less commonly, it may mimic vasculitic neuropathies or even present with overlapping motor symptoms. In our patient, the presence of leukopenia, skin rash, and chronic inflammatory CSF findings raised concern

Table 1. Comparative Summary of Clinical Features, Diagnostics, Treatments, and Outcomes in Two Patients with N_2O-Induced Neuropathy.

Characteristic	Case 1	Case 2
Age and Sex	34-male	52-female
Clinical Presentation	Ascending numbness, tingling, gait imbalance, frequent falls	Bilateral simultaneous painless foot drop, gait imbalance, numbness, balance issues
Onset & Duration	January 2024, progressive over several months	November 2024, subacute progression
Neurological Examination	Mild distal lower limb weakness, absent vibration at knees, proprioception impaired at toes, absent knee and ankle reflexes, wide-based gait	Severe distal lower limb weakness, absent vibration/proprioception at toes, hyperreflexia proximally, absent ankle reflexes, bilateral steppage gait
Relevant Medical History	Chronic back pain, previous alcohol dependence, recreational N_2O use	Breast cancer (chemotherapy/radiation), hypothyroidism, Sjogren's syndrome, chronic N_2O abuse
Vitamin B12 & MMA Levels	Vitamin B12: 123 pg/mL; MMA: 1.66 µmol/L	Vitamin B12: 111 pg/mL; MMA: 0.45 µmol/L
EMG/NCS Findings	Sensorimotor axonal neuropathy	Length-dependent pure motor axonal neuropathy
MRI Findings	Mild degenerative lumbar spine changes, No posterior column signal changes	Cervical stenosis with hazy increased cord signal. No spinal cord signal changes on lumbar MRI. (Figure 1)
Initial Diagnosis	CIDP	CIDP, small vessel vasculitis
Treatment Received	Vitamin B12 supplementation, cessation of nitrous oxide, physical therapy	Steroids, IVIG (no response), vitamin B12 supplementation, planned orthotic support
Clinical Outcomes	Significant symptomatic improvement, improved balance, mild residual symptoms	Modest improvement in balance and ambulation, persistent severe foot drop, ongoing evaluation

for autoimmune or vasculitic neuropathy. However, the electrophysiological pattern of a pure motor axonopathy, muscle and nerve biopsy findings, combined with a known history of nitrous oxide abuse and vitamin B12 deficiency, favored a toxic-metabolic etiology. This underscores the importance of integrating autoimmune markers with clinical, electrodiagnostic, and histopathologic data to avoid misclassification and unnecessary immunotherapy.[8]

Emerging literature highlights the mechanism by which N_2O remains stored in the body, contributing to ongoing neurological damage despite cessation of exposure. N_2O can bind intracellularly in a stabilized form known as dinitrosyl iron (II) complexes with protein thiols.[9] These complexes serve as reservoirs, thus gradually releasing N_2O-derived reactive species over the period of time. Such slow release can perpetuate vitamin B12 deficiency and subsequent neurotoxicity, explaining persistent symptoms and potential relapse after premature discontinuation of vitamin B12 supplementation.[9]

Given this pathophysiology, prolonged and adequately dosed vitamin B12 supplementation is essential. In our series, both patients received 1000 mcg of intramuscular vitamin B12 weekly for four weeks as part of the induction phase, followed by monthly 1000 mcg injections for

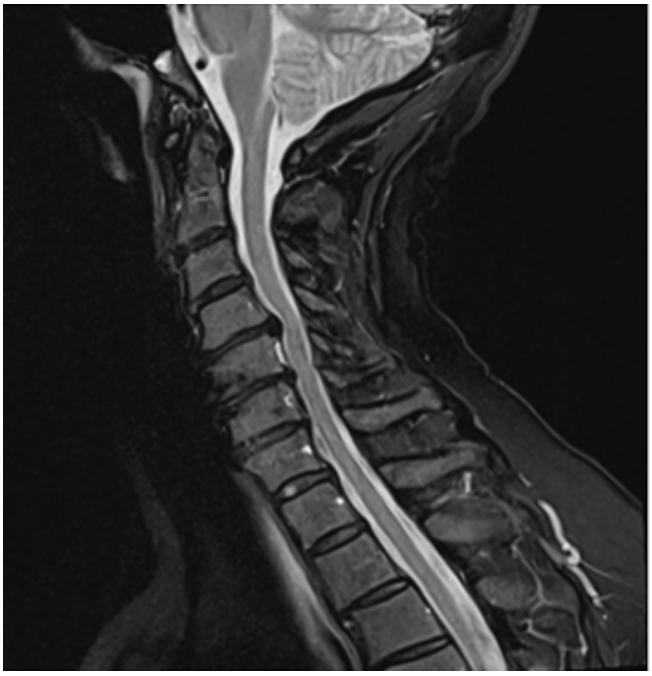

Fig 1: MRI C-spine sagittal view, STIR sequence. Showing cervical stenosis and hazy increased signal at the level of C4-5 C5-6 that might be due early myelomalacia.

maintenance, but in case 2 due to more advanced disease and delayed recognition, recovery was limited. Previous literature suggests that therapy should be continued for at least 6–12 months, and sometimes longer, based on clinical and biochemical response. Premature cessation may risk relapse due to continued oxidative inactivation of cobalamin by intracellularly stored N_2O complexes.[2,4] Our case series emphasizes this point, as seen in Case 1, where the patient who received consistent supplementation and ceased N_2O use early experienced marked clinical improvement. Conversely, the Case 2 patient, who had prolonged exposure and delayed diagnosis, showed minimal improvement which is likely due not only to the need for sustained long-term therapy but also to the greater severity of her initial neurological presentation including profound bilateral foot drop and pure motor axonopathy, compared to the milder, more sensory-predominant deficits observed in Case 1.

The diagnostic complexity in both cases highlights the potential overlap between nitrous oxide (N_2O) misuse and autoimmune conditions. N_2O-induced neuropathy, resulting from functional vitamin B12 inactivation, may mimic autoimmune neuropathies like Guillain-Barré syndrome, including features such as motor weakness and areflexia. Reports of positive anti-ganglioside antibodies in some cases suggest a possible immune-mediated component. In patients with underlying autoimmune disorders like Sjögren's syndrome, this overlap can complicate diagnosis.[8] Clinicians should consider N_2O-induced neuropathy in patients with acute or subacute neuropathic symptoms and relevant exposure history to avoid misdiagnosis and inappropriate treatment.[10] N_2O-induced neurotoxicity is classically associated with subacute combined degeneration of the spinal cord, primarily affecting the posterior columns, leading to sensory ataxia and proprioceptive loss. This myelopathic pattern is well documented and often visible as hyperintense signal changes in the dorsal cord on MRI.[3] However emerging evidence, including the present case series demonstrates that N_2O can also produce isolated peripheral neuropathies, particularly axonal or motor-predominant forms, even in the absence of spinal cord signal changes. This variability in localization complicates the clinical picture and may delay diagnosis if N_2O toxicity is not considered early. This case series also highlights the interplay between N_2O-induced neuropathy and coexisting autoimmune conditions, further complicating diagnosis and management. Notably, a significant proportion of patients with N_2O-induced neuropathy may have normal or borderline serum vitamin B12 levels despite functional deficiency. This occurs due to oxidation of cobalamin by N_2O, impairing its cofactor activity without reducing total serum levels. A systematic review by Oussalah et al. reported that approximately 30% of patients with N_2O-related toxicity had normal serum vitamin B_{12} concentrations, despite exhibiting clinical signs of deficiency.[11] In such cases, testing methylmalonic acid (MMA) and homocysteine provides more sensitive indicators of functional B12 status. Elevated levels of MMA or homocysteine should prompt consideration of N_2O-related neurotoxicity even when serum B12 appears normal, to avoid missed or delayed diagnosis.[3] Our clinical findings expand current understanding by illustrating real-world challenges clinicians face, particularly regarding the duration and monitoring of B12 therapy to mitigate relapse risk.

In conclusion, this case series demonstrates the importance of maintaining a high clinical suspicion for N_2O-induced neuropathy in patients presenting with idiopathic peripheral neuropathy, particularly those non-responsive to immunotherapy. Clinicians should recognize the potential for prolonged biological storage of N_2O in the form of stable dinitrosyl iron complexes, necessitating extended vitamin B12 supplementation for at least 6–12 months to prevent relapse. Additionally, comprehensive history taking regarding recreational substance use remains important for timely and accurate diagnosis.

Disclosure Statement

Ethical Approval: Not applicable

Funding Declaration: No funding was received for this report

Conflict of interests: The authors declare no conflict of interests

References

1. Kaar SJ, Ferris J, Waldron J, Devaney M, Ramsey J, Winstock AR. Up: The rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. Journal of psychopharmacology. 2016 Apr;30(4):395-401.
2. Zou X, Yi F, Zhou W, Dong Y, Alhaskawi A, Zhou H, Ezzi SH, Kota VG, Abdulla MH, Alenikova O, Abdalbary SA. Mechanisms and recent advances in the diagnosis and treatment of nitrous oxide-induced peripheral neuropathy: a narrative review. Frontiers in Neurology. 2024 May 23;15:1381938.
3. McCormick B, Thomas J, Patel R, Anderson N. Nitrous oxide-induced myeloneuropathy: an emerging public health issue. Neurology. 2023;101(14):e1567–75.
4. Singer MA, Lazaridis C, Nations SP, Wolfe GI. Reversible nitrous oxide-induced myeloneuropathy with pernicious anemia: case report and literature review. Muscle Nerve. 2007;36(5):614–6.
5. Berling I, Isbister GK, Grice J, Graudins A. Nitrous oxide-induced predominantly motor neuropathies: a follow-up study. Clin Toxicol (Phila). 2022;60(5):452–8.
6. Darmiga R, Patel N, Youngstein T. Nitrous oxide-induced neurotoxicity: a case report and literature review. BMJ Case Rep. 2021;14(6):e241279.
7. Mair D, Paris A, Zaloum SA, White LM, Dodd KC,

Englezou C, Patel F, Abualnaja S, Lilleker JB, Gosal D, Hayton T, Liang D, Allroggen H, Pucci M, Keddie S, Noyce AJ. Nitrous oxide-induced myeloneuropathy: a case series. J Neurol Neurosurg Psychiatry. 2023 Sep;94(9):681-688.

8. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, Katsuno M, Fujita A, Aiba I, Ogata A, Saito T. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. Brain. 2005 Nov 1;128(11):2518-34.
9. Mülsch A, Busse R. The potent vasodilating and guanylyl cyclase-activating dinitrosyl-iron(II) complex is stored in a protein-bound form and released by thiols. Eur J Pharmacol. 1991;202(1):97–102.
10. Dong MX, Wang Q, Xu JF, Hu L, Yu Y, Li T. Case report: Recreational nitrous oxide abuse triggered peripheral neuropathy possibly through the immune-mediated pathogenesis. Frontiers in Neurology. 2022 Nov 14;13:1033327.
11. Oussalah A, Julien M, Levy J, Hajjar O, Franczak C, Stephan C, Laugel E, Wandzel M, Filhine-Tresarrieu P, Green R, Guéant JL. Global burden related to nitrous oxide exposure in medical and recreational settings: a systematic review and individual patient data meta-analysis. Journal of clinical medicine. 2019 Apr 23;8(4):551.

POEMS Syndrome: A Case Highlighting the Challenges in Diagnosis

Syed M. Ahmed DO & Long Davalos MD

Department of Neurology, Neuromuscular Division,
University of Kansas Medical Center

Abstract

POEMS syndrome is a multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, and skin changes in the context of a monoclonal plasma cell disorder. While these features may appear in the syndrome, they do not always occur simultaneously and can present with multiple other symptoms. A thorough laboratory and radiological workup is recommended to assess for multisystem involvement, and a bone marrow or skeletal lesion biopsy may be necessary to confirm an underlying plasma cell disorder. Given the wide range of possible presentations, diagnosing POEMS can be challenging and may be confused with CIDP or smoldering myeloma. However, maintaining a high clinical suspicion this syndrome, even when not all features are present, is crucial for a timely diagnosis and optimal treatment, particularly for neurological recovery. We present the case of a 57-year-old male with progressive sensorimotor weakness who was initially diagnosed with CIDP but ultimately found to have POEMS syndrome, based on elevated VEGF levels, IgG lambda monoclonal gammopathy, sclerotic bone lesions, skin changes, endocrinopathy, and a biopsy-proven plasmacytoma.

Introduction

POEMS syndrome is a paraneoplastic, multisystem disorder that occurs in the setting of an underlying plasma cell disorder.[1] Although the acronym implies the presence of polyneuropathy, organomegaly, endocrinopathy, a monoclonal plasma cell disorder, and skin changes, not all of the features may be present, nor are they required to make the diagnosis.[2] Other features, such as elevated vascular endothelial growth factor (VEGF) levels, sclerotic bone lesions, Castleman disease, extravascular volume overload, and papilledema, may accompany the polyneuropathy and underlying monoclonal disorder and help fulfill the major and minor criteria to make the diagnosis (Table 1).

A thorough evaluation, including skin inspection, laboratory workup and testing such as a skeletal survey and bone marrow biopsy, is crucial to differentiate the syndrome from chronic inflammatory demyelinating polyneuropathy (CIDP), isolated monoclonal gammopathy of uncertain significance (MGUS), or smoldering multiple myeloma. This is important to avoid unnecessary treatment-related adverse events and to prevent further progression due to undertreatment. In this report, we present the case of a 57-year-old male with rapidly progressive demyelinating polyneuropathy, who was eventually diagnosed with POEMS syndrome, highlighting the diagnostic challenges associated with this condition.

Table 1. Diagnosis criteria for POEMS syndrome

Mandatory Major Criteria	Polyneuropathy (typically demyelinating)
	Monoclonal plasma cell-proliferative disorder (almost always λ)
Other Major Criteria	Castleman disease
	Sclerotic bone lesions
	Vascular endothelial growth factor elevation
Minor Criteria	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	Extravascular volume overload (edema, pleural effusion, or ascites)
	Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	Papilledema
	Thrombocytosis/polycythemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values

*Both mandatory major criteria, one other major criterion, and one minor criterion need to be present to confirm the diagnosis

Case

A 57-year-old male with a 20-year history of rheumatoid arthritis (RA) presented with rapidly progressive weakness and numbness. Initially, he reported intermittent paresthesias in his soles. Over the next 4 months, he experienced mild difficulties with thumb extension and ankle plantar flexion. He developed bilateral foot drop, which progressed rapidly to complete ankle and toe paralysis over 2 months. During this time, he also experienced finger extension weakness, difficulty standing from a seated position, intense paresthesias and numbness in his hands and feet, and increasing difficulty with ambulation, eventually requiring a walker. He denied ocular, bulbar, respiratory, or autonomic symptoms, as well as pain. He reported an unintentional 40-pound weight loss over 6 months but no fever or night sweats. His RA had been well-controlled for years without recent medication or flare-ups. He was diagnosed with diabetes (hemoglobin A1C 7.2%) a few weeks earlier, as part of a neuropathy work-up.

On examination, he had moderate weakness in proximal muscles (Medical Research Council [MRC] scale 3 to 4) and severe weakness in distal upper extremity (MRC scale 1 to 2) and lower extremity (MRC scale 0) muscles. Sensory examination revealed absent vibration and proprioception at the ankles, and absent proprioception at the metacarpophalangeal joint, with decreased vibration at the wrist. Pinprick sensation was normal, and he had diffuse areflexia. He was unable to maintain a standing position and required a walker to ambulate.

Electrodiagnostic testing revealed a primarily demyelinating sensorimotor polyradiculoneuropathy with secondary axonal loss. The nerve conduction studies (NCS) showed severe axonal loss in the lower extremities and moderate axonal loss with prolonged latency, slowed conduction velocity, conduction block of greater than 30% and temporal dispersion in the right median and ulnar motor nerves (Table 2). There was active denervation in the distal muscles tested (Table 3).

Findings met definite 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) CIDP electrodiagnostic criteria. Based on clinical presentation and electrodiagnostic findings, he was diagnosed with severe CIDP and was admitted for plasma exchange (PLEX).

Initial laboratory testing revealed a hemoglobin A1C of 7.2%, and an IgG lambda monoclonal gammopathy of 0.44 g/dL. Kappa and lambda light chains, and the free light chain (FLC) ratio were normal. VEGF was elevated at 446 pg/mL (normal range: 9–86 pg/mL). Otherwise, the sedimentation rate, C-reactive protein (CRP), TSH, vitamin B1 and B12, copper levels, complete blood count, and comprehensive metabolic panel were normal. Based on the laboratory results and the presence of demyelinating polyneuropathy, there was concern for POEMS syndrome.

Skin inspection revealed glomeruloid hemangiomata on the abdomen and peripheral edema in the lower extremities. A computed tomography (CT) scan of the chest, abdomen, and pelvis, with and without contrast, showed mixed lytic and sclerotic osseous lesions in the S1 and S2 sacral segments (Figure 1), as well as multiple small pelvic lymph nodes (within normal size limits) and small soft tissue retroperitoneal nodules.

Table 2. Nerve conduction study

Motor Nerve Conductions							
Nerve/Site	**Latency (ms)**	**Amplitude (mV)**	**Duration (ms)**	**Segments**	**Distance (mm)**	**Latency difference (ms)**	**CV (m/s)**
R Median-ABP							
Wrist	5.6	1.9	8.2	Wrist-ABP	70	5.6	
Elbow	21.1	1.3	11.7	Elbow-Wrist	270	15.5	17
R Ulnar-ADM							
Wrist	5.2	3.0	8.5	Wrist-ADM	70	5.2	
B. Elbow	12.9	2.0	23.5	B. Elbow-Wrist	210	7.6	27
A. Elbow	16.3	1.5	22.4	A. Elbow-B. Elbow	100	3.4	30
R Peroneal- EDB							
Ankle	NR	NR	NR	Ankle-EDB	80	NR	
R Peroneal- TA							
B. Fibular Head	NR	NR	NR	B. Fibular head-TA		NR	
R. Tibial- AH							
Ankle	Ankle	NR	NR	Ankle-AH	80	NR	
F Waves							
Nerve	**M Latency (ms)**			**F latency (ms)**			
R Median- ABP	NR			NR			
R Ulnar- ADM	NR			NR			
Sensory Nerve Conductions							
Nerve/Site	**Onset Latency (ms)**	**Peak Latency (ms)**	**Amplitude (uV)**	**Segments**	**Latency difference (ms)**	**Distance (mm)**	**CV (m/s)**
R Median-antidromic							
Wrist	3.6	4.4	5.4	Wrist- Digit II	3.56	130	36.5
R Ulnar-Antidromic							
Wrist	NR	NR	NR	Wrist- Digit V	NR	110	NR
R Radial-Anatomic Snuffbox							
Forearm	2.6	3.4	8.7	Forearm-Snuffbox	2.56	100	39.0
R Sural-Calf							
Lower leg	NR	NR	NR	Lower leg-ankle	NR	140	NR

* The upper and lower extremity temperature for this study was 32 ^{0}C
Abbreviations: ms, millisecond; mV, millivolts; mm, millimeter; m/s, meters per second; ABP, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; TA, tibialis anterior; AH, abductor hallucis; R, right; A, above; B, below; NR, no response

Table 3. Electromyography study

EMG Summary Table									
	Insertional	Spontaneous Activity			Volitional MUAPs				
Muscle	**Activity**	**Fibs**	**PSW**	**Fasc**	**Poly**	**Amp**	**Duration**	**Recruitment**	**Other**
R Tibialis Anterior	++	3+	3+	None					No MUPs observed
R Gastrocnemius	++	3+	3+	None					No MUPs observed
R Vastus medialis	++	3+	3+	None	++	Normal	+	Moderately decreased	None
R First Dorsal Interosseous	++	3+	3+	None	None	Normal	Normal	Severely decreased	None
R Deltoid	Normal	None	None	None	None	Normal	Normal	Moderately decreased	None

* Abbreviations: R, right; MUAP, motor unit action potentials; MUPs, motor unit potentials; Fibs, fibrillation potentials; PSW, positive sharp waves; Fasc, fasciculations; Poly, polyphasic potentials; Amp, amplitude

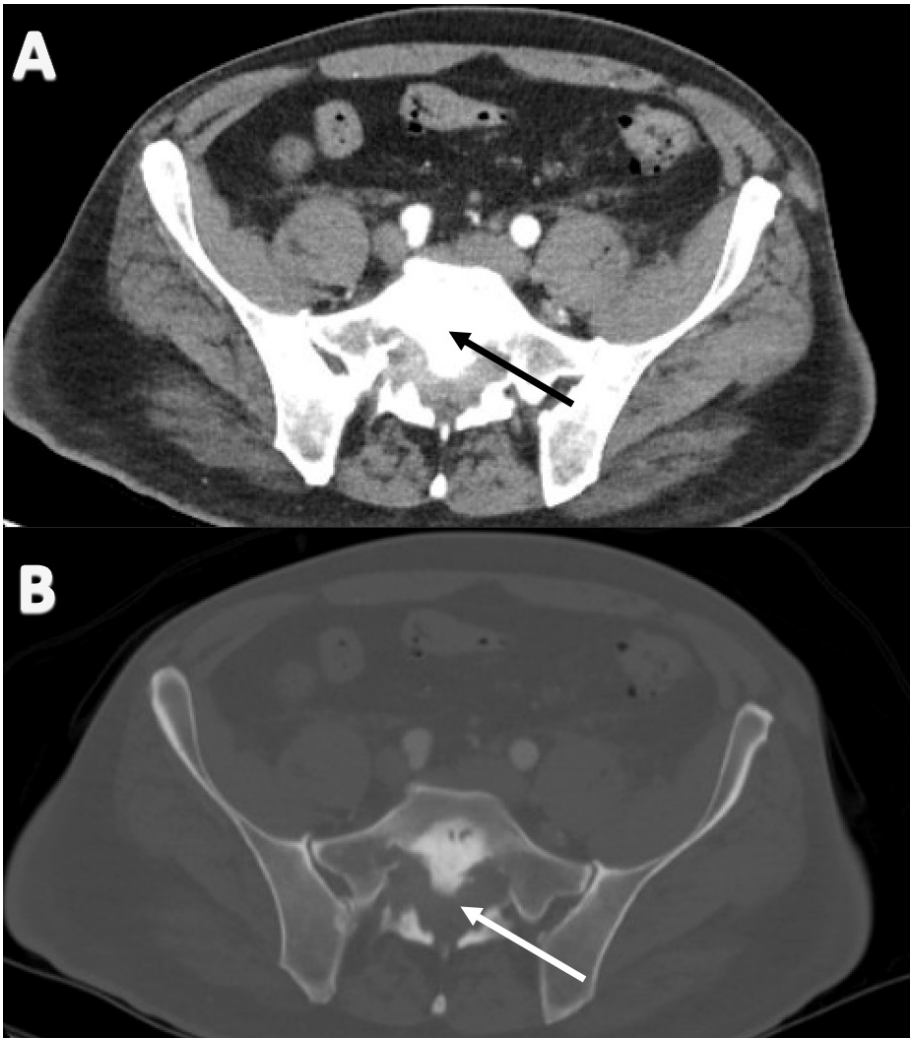

Figure 1: Computed tomography scan of the sacrum depicting mixed lytic and sclerotic lesions of the S1 and S2 sacral body. (A) Sclerotic component of the sacral body as noted by the hyperdense region (*black arrow*). (B) Lytic component of the sacral body as noted by the hypodense region (*white arrow*)

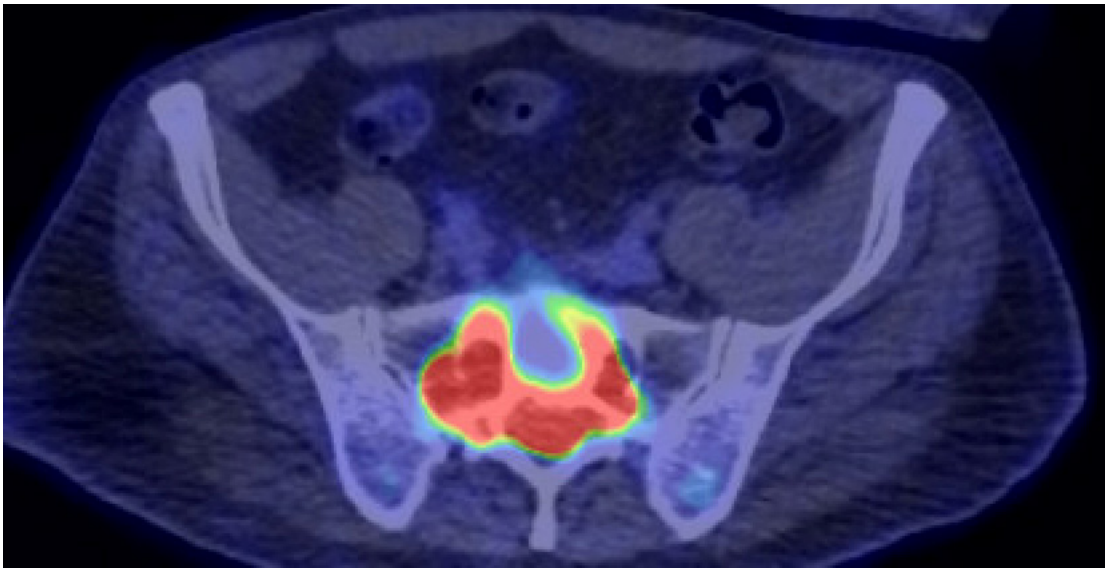

Figure 2: Nuclear medicine position emission tomography scan depicting increased fluorodeoxyglucose uptake involving the sacral lytic lesion.

Endocrinology labs revealed mild prolactin elevation and low testosterone levels. However, given the absence of symptoms and in the context of an acute illness, the endocrinology team did not consider these laboratory abnormalities clinically relevant to support a diagnosis of POEMS syndrome. A bone marrow biopsy was normal, and because of this, along with the lack of organomegaly and small paraprotein level, the hematology team was hesitant to diagnose POEMS syndrome.

A PET scan showed increase FDG uptake involving the lytic lesion mentioned (Figure 2), but no other areas of concern. The patient completed 5 sessions of PLEX with mild proximal strength improvement but worsening of finger extension and abduction strength. A biopsy of the sacral lytic lesion eventually revealed monoclonal lambda plasma cells, after which it was decided to proceed with radiotherapy targeting the isolated lytic lesion.

Discussion

Diagnosing POEMS syndrome can be challenging, but maintaining a high suspicion in patients with progressive sensorimotor demyelinating polyneuropathy and paraproteinemia, especially if refractory to immunotherapy, is crucial for ensuring appropriate and prompt treatment. Our patient met mandatory criteria for diagnosis (polyneuropathy and a monoclonal plasma cell proliferative disorder) along with two major criteria (elevated VEGF levels and sclerotic bone lesions) and two minor criteria (skin changes and peripheral edema – diabetes is not sufficient to fulfill the endocrinopathy criteria), thus confirming the diagnosis.[2]

One challenge in diagnosing POEMS is the misconception that patients must present all components of the acronym. The only mandatory features are polyneuropathy and a monoclonal plasmaproliferative disorder. In most cases, the polyneuropathy is progressive, length-dependent, sensorimotor, and refractory to immunotherapy, with electrodiagnostic testing showing demyelination and secondary axonal loss.[1] Compared to CIDP, NCS in POEMS typically shows greater axonal loss, more pronounced slowing of motor and sensory conduction velocities, less frequent temporal dispersion and conduction block, and absence of sural sparing.[1,3] Interestingly, the NCS of our patient showed temporal dispersion and conduction block. Although these findings are unusual in POEMS, their presence should not deter consideration of this diagnosis.

The monoclonal (M)-protein is almost always IgA or IgG lambda. In about 78% of cases, FLC ratio is normal, and the M-spike is usually small.[1,2] In one case series, the median paraprotein level was 1.1 g/dL, with 93% of patients having an M-spike of 2 g/dL or less, as in our case.[4] This is significant because an IgG M-protein level below 1.5 g/dL with a normal FLC ratio is considered low-risk for multiple myeloma and may be overlooked.[5]

The other features of the POEMS acronym are non-mandatory. Organomegaly affects 45% to 85% of patients and, when present, is typically mild.[2] Hemangiomas or telangiectasia occur in 9% to 35% of patients, as in our case, while other skin manifestations, such as hyperpigmentation, plethora, acrocyanosis, and hypertrichosis, are seen in 68% to 93% of cases.[2] Endocrinopathies are present in 66-96% of cases, with hypogonadism being the most common.[6] While diabetes is not considered part of the criteria due to its high prevalence in the general population, the new onset of diabetes coinciding with severe progressive neuropathy in our case suggests it is related to POEMS.

VEGF testing is a key diagnostic tool for identifying POEMS syndrome, with a cutoff of 200 pg/mL demonstrating 95% specificity and 98% sensitivity. It may

be cost-effective to test all patients with CIDP, as testing only refractory cases might be too little, too late.[7] Bone marrow aspirate and biopsy are also essential. Biopsy findings typically include megakaryocyte hyperplasia, clustering, and clonal plasma cells.[2] However, one-third of patients, particularly those with solitary or multiple solitary plasmacytomas, may have normal results.[1,2] In contrast, biopsy of bone lesions is abnormal in 90% of cases, showing diffuse infiltration of light chain-restricted plasma cells. This provides a high yield for identifying monoclonal plasma cells, especially when bone marrow biopsy results are inconclusive, as in our case.[1,2]

The use of modern therapies for POEMS, including radiation therapy, chemotherapy, and autologous stem cell transplant (ASCT), has led to relatively favorable outcomes. Ten-year survival data show a 24% improvement, with survival increasing from 55% in patients diagnosed before 2004 to 79% in those diagnosed after.[2] Neurological response is typically observed 6 months after completing therapy.

Treatment recommendations are based on bone marrow involvement. A curative response may be achieved with radiation therapy for isolated bone lesions. In patients with bone marrow involvement, systemic therapy may be recommended, with or without radiation, depending on the characteristics of the bone lesion (size and lytic component).[2] Our patient has an isolated bone lesion without clonal plasma cells on the bone marrow biopsy. In this population, targeted radiation leads to a 4-year overall survival rate of 97% and a 10-year overall survival rate of 70%, indicating a favorable prognosis.[8]

Citation

1. Keddie S, Foldes D, Caimari F, Baldeweg SE, Bomsztyk J, Ziff OJ, Fehmi J, Cerner A, Jaunmuktane Z, Brandner S, Yong K, Manji H, Carr A, Rinaldi S, Reilly MM, D'Sa S, Lunn MP. Clinical characteristics, risk factors, and outcomes of POEMS syndrome: A longitudinal cohort study. Neurology. 2020 Jul 21;95(3):e268-e279. doi: 10.1212/WNL.0000000000009940. Epub 2020 Jun 30. PMID: 32606227.
2. Dispenzieri A. POEMS syndrome: Update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 Dec;98(12):1934-1950. doi: 10.1002/ajh.27081. Epub 2023 Sep 21. PMID: 37732822.
3. Mauermann ML, Sorenson EJ, Dispenzieri A, Mandrekar J, Suarez GA, Dyck PJ, Dyck PJ. Uniform demyelination and more severe axonal loss distinguish POEMS syndrome from CIDP. J Neurol Neurosurg Psychiatry. 2012 May;83(5):480-6. doi: 10.1136/jnnp-2011-301472. Epub 2012 Mar 6. PMID: 22396441.
4. Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therneau TM, Larson DR, Greipp PR, Witzig TE, Basu R, Suarez GA, Fonseca R, Lust JA, Gertz MA. POEMS syndrome: definitions and long-term outcome. Blood. 2003 Apr 1;101(7):2496-506. doi: 10.1182/blood-2002-07-2299. Epub 2002 Nov 27. PMID: 12456500.
5. Hillengass J, Usmani S, Rajkumar SV, Durie BGM, Mateos MV, Lonial S, Joao C, Anderson KC, García-Sanz R, Riva E, Du J, van de Donk N, Berdeja JG, Terpos E, Zamagni E, Kyle RA, San Miguel J, Goldschmidt H, Giralt S, Kumar S, Raje N, Ludwig H, Ocio E, Schots R, Einsele H, Schjesvold F, Chen WM, Abildgaard N, Lipe BC, Dytfeld D, Wirk BM, Drake M, Cavo M, Lahuerta JJ, Lentzsch S. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol. 2019 Jun;20(6):e302-e312. doi: 10.1016/S1470-2045(19)30309-2. Erratum in: Lancet Oncol. 2019 Jul;20(7):e346. doi: 10.1016/S1470-2045(19)30423-1. PMID: 31162104.
6. Li H, Huang Y, Li Y, Zheng B, Cui J, Liu M. Endocrine Manifestations in POEMS Syndrome: a case report and literature review. BMC Endocr Disord. 2019 Mar 22;19(1):33. doi: 10.1186/s12902-019-0355-6. PMID: 30902082; PMCID: PMC6431048.
7. Marsh ES, Keddie S, Terris-Prestholt F, D'Sa S, Lunn MP. Early VEGF testing in inflammatory neuropathy avoids POEMS syndrome misdiagnosis and associated costs. J Neurol Neurosurg Psychiatry. 2021 Feb;92(2):172-176. doi: 10.1136/jnnp-2020-324012. Epub 2020 Oct 26. PMID: 33106368.
8. Kourelis TV, Buadi FK, Kumar SK, Gertz MA, Lacy MQ, Dingli D, Go RS, Kapoor P, Lust JA, Hayman SR, Hwa Y, Rajkumar SV, Zeldenrust SR, Russell SJ, Lin Y, Leung N, Kyle RA, Gonsalves WI, Dispenzieri A. Long-term outcome of patients with POEMS syndrome: An update of the Mayo Clinic experience. Am J Hematol. 2016 Jun;91(6):585-9. doi: 10.1002/ajh.24356. Epub 2016 Apr 13. PMID: 26972803.

A case of eculizumab-induced hemophagocytic lymphohistiocytosis (HLH) in a myasthenia gravis patient

Salma S. Elkolaly MD[1], Dinanath P. Attele DO[2], Erik R. Ensrud MD[1]

[1] Department of Neurology, University of Missouri, Columbia, Missouri, USA
[2] Department of Neurology, University of Utah, Salt Lake City, Utah, USA

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an immune hyperactivation state that can occur in immunosuppressed patients and is associated with high mortality and worse prognosis. We present a case of 78-year-old patient on multiple immune suppressing medications, including eculizumab and azathioprine for myasthenia gravis, who presented to our hospital for evaluation of hyperbilirubinemia. She had extensive laboratory workup that was significant for anemia, thrombocytopenia, increased ferritin level, and hyponatremia. Additionally, she had increased CD25 and CXCL9 leading to the diagnosis of HLH. Investigations for triggering factors identified eculizumab after excluding multiple infectious and rheumatologic conditions. Unfortunately, the patient did not survive. We recommend evaluating for high ferritin as a reliable predictor for HLH for patients on myasthenia gravis on eculizumab.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening immune response caused by hyperactivation of macrophages and cytotoxic T-lymphocytes. Due to the lack of down-regulation of these immune cells, cytokine storm with variable interleukins can cause multi-organ failure.[1] The triggers for HLH are still not fully understood. However, it is now known that the triggers can range from hyper-immune states such as Epstein-Barr virus to immune-suppressed states such as human immunodeficiency virus, malignancy and inherited immune deficiency disorders.[2-3] Drug-induced HLH has been reported as an immune-related adverse effect (irAE) from few drugs such anti-PD1 and anti-CTLA-4 cancer immunotherapy.[4] There were reports of eculizumab therapy being associated with meningococcal infection and other infections as possible adverse events.[5] However, there is no published literature about HLH as an irAE of eculizumab. We present a case of a myasthenia gravis (MG) patient on eculizumab who developed HLH after an extensive workup to exclude any other possible triggers.

Case description

A 78-year-old female who presented to our hospital from an outside institution for evaluation of a pancreatic cancer found on her magnetic resonance cholangiopancreatography (MRCP). The patient initially presented to the outside hospital with a two-week history of jaundice; MRCP revealed pancreatic divisium and pancreatic duct dilation concerning for cancer. Upon presenting to our hospital, our gastroenterology service was consulted, and recommended a second read of the MRCP. Surprisingly, the second read did not show any evidence of pancreatic duct dilation, common bile duct dilation or pancreatic cancer. Instead, it showed multiple hepatic cysts and splenomegaly (Figure 1).

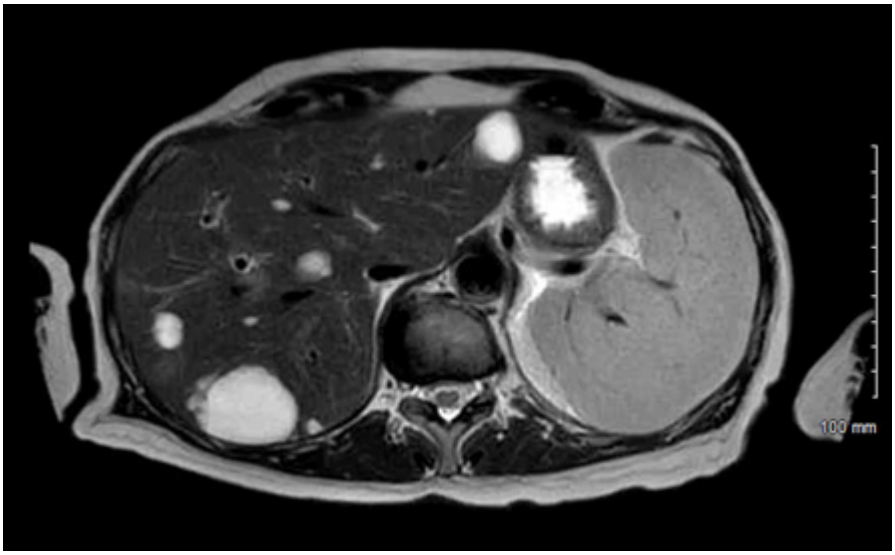

Figure 1. Multiple hepatic cysts and splenomegaly demonstrated on magnetic resonance cholangiopancreatography

Upon further history taking, patient reported having three days of sore throat and fever before her jaundice started. She reported occasional nausea, but no vomiting or abdominal pain. She denied any recent travels, illnesses, or medications. She reported a past medical history of remote seizure on phenytoin, thalassemia with no prior transfusions, and MG being treated with prednisone, pyridostigmine, azathioprine, and biweekly eculizumab infusions. She was diagnosed with MG in 2008. She was initially started on azathioprine, then started on eculizumab in 2020 with her last dose on the day prior to admission. When evaluated by the inpatient neurology service, there was no noticeable weakness in bilateral upper and lower extremities. However, she had an element of fatiguability on some provocative maneuvers. She was continued on eculizumab during hospitalization, but azathioprine was stopped given concern of liver injury.

Physical examination was negative for pertinent signs except for severe jaundice. Vital signs were stable except for occasional spiking fevers with Tmax of 38.6°C. Labs were significant for low white blood cells 3.4 X10 (9)/ L, low hemoglobin 7.3 g/dL, low mean corpuscular volume 64.1 fL, low platelet count 103 x 10^9/L, low sodium of 126 mmol/L and total bilirubin of 15.03 mg/dL. Infectious Disease service and Hematology-Oncology service were consulted for evaluation of infectious causes of hyperbilirubinemia and thrombocytopenia, respectively. Nephrology service was consulted for management of hyponatremia after initial attempts to correct by primary team. To simplify the presentation of our diagnostic approach, all workup performed by the primary team and consult services are presented in Figure 2 . After an extensive week-long workup during hospitalization, infectious etiology was ruled out. HLH was suspected at this time, and soluble CD25 (soluble IL-2 receptor) and CXCL-9 were ordered. They came back high at 8288 pg/ml and 15,989 pg/ml, respectively. At this point, the patient was transferred to another tertiary center for further evaluation and consideration of liver transplantation. Results were communicated, and patient was started on etoposide after transfer. However, the patient passed away after around two weeks of transfer. Cause of death was communicated to be related to HLH.

Discussion

Eculizumab is a humanized monoclonal antibody that works against complement factor 5 to prevent the complement fixation of acetyl-choline receptor antibodies in seropositive MG patients.[6-7] Per the American Academy of Neurology guidelines, eculizumab is indicated in severe, refractory seropositive MG after unsuccessful trials of other immunologic agents.[8] There is no published literature on the long-term safety profile of eculizumab in MG patients; however, it is reportedly generally well-tolerated. Frequent reported adverse effects include headache and upper respiratory tract infection. Less common but serious adverse effects include MG crisis and exacerbation. To our knowledge, there are no published reports whether eculizumab can trigger HLH. On the contrary, eculizumab has been reported as a treatment for complement-mediated thrombotic microangiopathy (TMA) in case series of refractory HLH with complete resolution of their symptoms. It was reported by the authors that eculizumab probably worked against the activated complements implemented in TMA.[8]

HLH is a primarily pediatric disorder which certain genetic predispositions can trigger its primary form. Recurrent attacks could be expected in primary HLH. In the adult population, secondary HLH is more common in states of immunosuppression or conversely, hyperactivation with viruses or infections.[9] In our patient's case, an extensive workup was able to rule out infectious causes of hyperbilirubinemia, elevated liver enzymes or pancytopenia. However, she was immunosuppressed in the setting of prednisone, azathioprine, and eculizumab intake. Azathioprine was discontinued upon admission, but her course was progressive. She did not develop any of her symptoms in the past, so HLH recurrence from a primary source was excluded. The only association in her case with HLH was the eculizumab.

Perhaps, earlier diagnosis could be anticipated in the setting of high ferritin. In a large pediatric study in Texas, a ferritin level higher than 10,000 mg/L had a high sensitivity and specificity for HLH diagnosis of 90% and 98%, respectively.[10] In adults, there was a lower reported sensitivity of 28% with ferritin greater than 10,000 mg/L.[11] Ferritin was independently associated with higher mortality in HLH patients.[12]

Conclusion

We recommend paying further attention to serum ferritin as a predictor of HLH and report that eculizumab therapy can be a possible etiology.

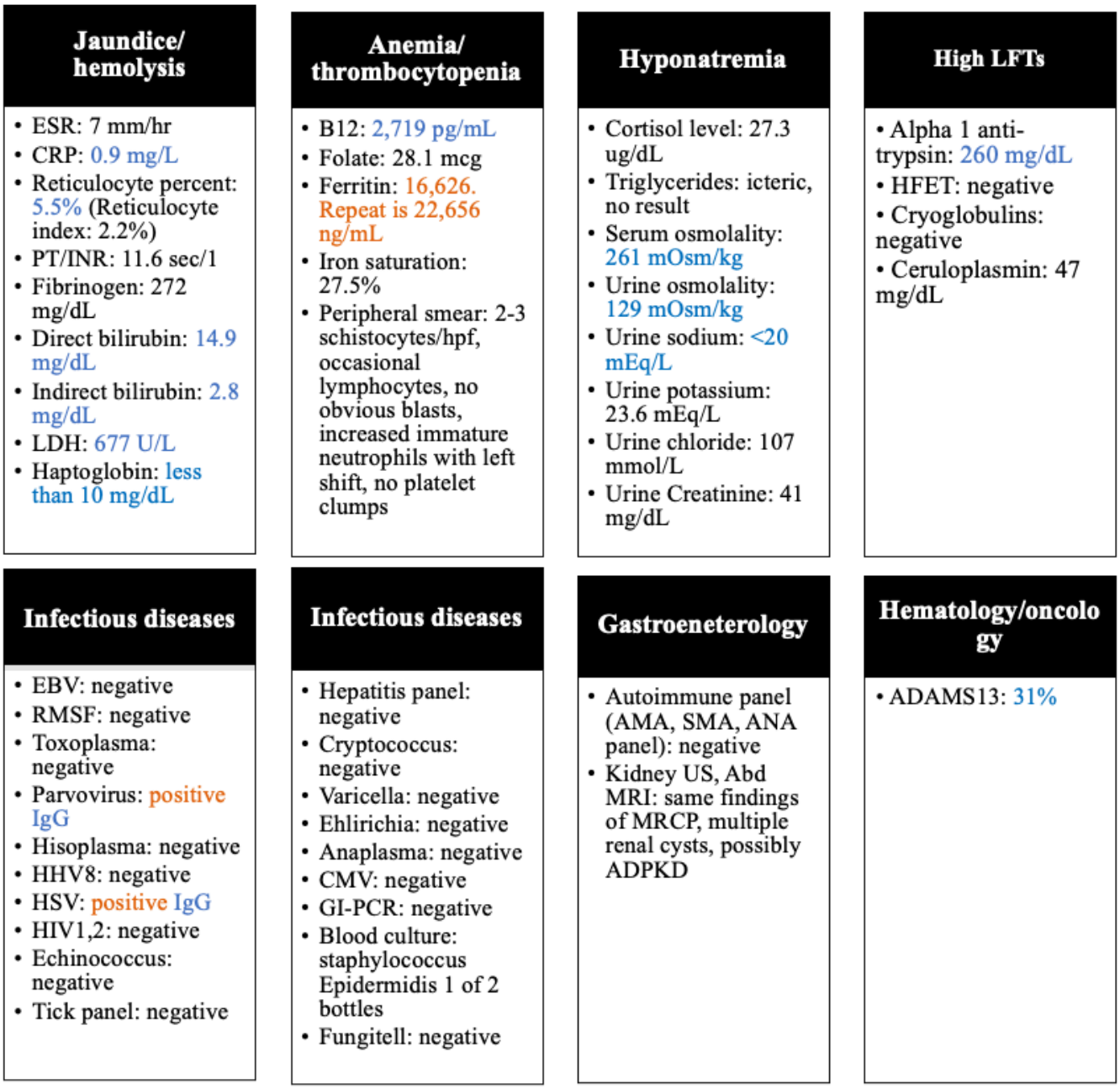

Figure 2. Above row indicates workup done for pertinent findings. Below row indicates workup by consulting services. Results in orange color indicates higher than normal values, and results in blue color indicates lower than normal values. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PT: prothrombin time, INR: international normalized ration, LDH: lactate dehydrogenase, EBV: Epstein-Barr virus, RMSF: rocky mountain spotted fever, HHV8: human herpesvirus 8, HSV: herpes simplex virus, HIV: human immunodeficiency virus, CMV: cytomegalovirus, GI-PCR: gastrointestinal polymerase chain reaction, AMA: antimitochondrial antibody, SMA: smooth muscle antibody, ANA: antinuclear antibody, US: ultrasound, MRI: magnetic resonance imaging, MRCP: magnetic resonance cholangiopancreatography, ADPKD: autosomal dominant polycystic kidney disease.

References

1. Filipovich A, McClain K, Grom A. Histiocytic Disorders: Recent Insights into Pathophysiology and Practical Guidelines. Biol Blood Marrow Transplant [Internet]. 2010 Jan 1;16(1):S82–9. Available from: https://doi.org/10.1016/j.bbmt.2009.11.014
2. Tabaja H, Kanj A, El Zein S, Comba IY, Chehab O, Mahmood M. A Review of Hemophagocytic Lymphohistiocytosis in Patients With HIV. Open forum Infect Dis. 2022 Apr;9(4):ofac071.
3. Bode SF, Ammann S, Al-Herz W, Bataneant M, Dvorak CC, Gehring S, et al. The syndrome of hemophagocytic lymphohistiocytosis in primary immunodeficiencies: implications for differential diagnosis and pathogenesis. Haematologica. 2015 Jul;100(7):978–88.
4. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin [Internet]. 2020 Mar 1;70(2):86–104. Available from: https://doi.org/10.3322/caac.21596
5. Howard Jr JF, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol [Internet]. 2017 Dec 1;16(12):976–86. Available from: https://doi.org/10.1016/S1474-4422(17)30369-1
6. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Nat Biotechnol. 2007 Nov;25(11):1256–64.
7. Dhillon S. Eculizumab: A Review in Generalized Myasthenia Gravis. Drugs. 2018 Mar;78(3):367–76.
8. Gloude NJ, Dandoy CE, Davies SM, Myers KC, Jordan MB, Marsh RA, et al. Thinking Beyond HLH: Clinical Features of Patients with Concurrent Presentation of Hemophagocytic Lymphohistiocytosis and Thrombotic Microangiopathy. J Clin Immunol. 2020 Jul;40(5):699–707.
9. Gupta S, Weitzman S. Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. Expert Rev Clin Immunol. 2010 Jan;6(1):137–54.
10. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008 Jun;50(6):1227–35.
11. Basu S, Maji B, Barman S, Ghosh A. Hyperferritinemia in Hemophagocytic Lymphohistiocytosis: A Single Institution Experience in Pediatric Patients. Indian J Clin Biochem. 2018 Jan;33(1):108–12.
12. Grangé S, Buchonnet G, Besnier E, Artaud-Macari E, Beduneau G, Carpentier D, et al. The Use of Ferritin to Identify Critically Ill Patients With Secondary Hemophagocytic Lymphohistiocytosis. Crit Care Med. 2016 Nov;44(11):e1045–53.

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She Is

Michael G. Abraham MD

Snow falling gently down her shoulders in beauty found.
A resting place, a reprieve from the cold North face.
Midnight searching for a space to be broken,
Her light shining between the shadows and pining.

Sunlight breaking through the cherry blossom flowers
Resting on her cool graceful face.
She looks up and down and turns all around
And shares her glow with the falling rays of bows.

Cotton candy clouds floating down so proud,
Kissing her cheeks while she bats her eyes and seeks.
Swirls and kisses around this missus.
White and blue, create reflections in her milieus.

Colors floating all around her like leaves in Fall.
Spinning fairies orbit her aura, the spring greeting her with its flora.
The Sun and the Moon, they compete to watch over her room.
The wind carries her a melody, her voice like that needed remedy.

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