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Mercury poisoning-associated membranous nephropathy and autoimmune encephalitis

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Abstract

Mercury intoxication is not uncommon and often presents with diverse symptoms of multiple systems. While neurological disorders and renal impairments have been examined in isolation, the concurrent occurrence of systemic symptoms linked to immune dysregulation is infrequently observed. Here, we report an unusual case that a 55-year-old male patient, who is a scrap merchant, was admitted to our center for neuropsychiatric disturbances, including incoherent speech and hallucinations. He was initially diagnosed with autoimmune encephalitis (AE) because of double positivity for CASPR2 and LGI1 antibodies in serum. The patient later presented with pruritus and nephrotic syndrome, where renal biopsy revealed membranous nephropathy (MN). In view of the mercury exposure history and elevated urinary mercury level, AE and MN were suspected to be related to mercury poisoning. The patient achieved a full recovery following a four-month treatment regimen comprising immunosuppressants and mercury-chelating agents, underscoring the significance of recognizing environmental toxins such as mercury in the coexisting diseases of different systems such as AE and MN.

Keywords Membranous nephropathy, Autoimmune encephalitis, Mercury poisoning, Case report

Introduction

Chronic mercury poisoning due to occupational exposure is common yet often overlooked. It can manifest as a spectrum of clinical symptoms, including neuropsychiatric manifestations, oral mucosal lesions, renal impairments, and multiorgan system involvement. It is challenging for clinicians to promptly identify heavy metal poisoning because of its obscure exposure history, atypical clinical presentation, and perplexing examination findings. The final diagnosis of chronic mercury poisoning is usually reached after the limited effectiveness of conventional treatments targeting a single system, prompting a more thorough investigation of the patient's personal history and a comprehensive assessment.

Autoimmune encephalitis (AE) is an autoimmune disorder characterized by inflammation of the brain in the absence of a known infectious or structural cause. The diagnosis of AE relies on the detection of autoantibodies targeting the brain in serum or cerebrospinal fluid (CSF). Nephrotic syndrome (NS), also largely attributed to immune system dysregulation, is characterized by heavy proteinuria, hypoalbuminemia, and edema. The concurrence of multisystemic pathologies against the backdrop of immune disorders is a frequently encountered scenario. In the context of mercury poisoning, the most common pathological type of NS is membranous nephropathy (MN). In this report, we present the case of a 55-year-old male who presented with pruritus, AE and MN along with a history of mercury exposure. This

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case highlights the importance of a thorough occupational and environmental history-taking in the diagnostic workup of patients presenting with unexplained multisystemic lesions, especially those linked to autoimmune dysregulation.

Case report

A 55-year-old male, a scrap merchant, presented to our neurology department on two occasions with recurrent complaints of nonsense disorders, accompanied by hallucinations, lethargy, social withdrawal, and anxiety.

First admission

The patient was initially hospitalized due to the ineffectiveness of a one-day trial of antipsychotic medication (Chlorpromazine 25 mg, administered twice daily) prescribed at an external psychiatric facility. This regimen was discontinued upon admission. A head magnetic resonance imaging (MRI) scan did not yield any abnormalities, and chest CT imaging only showed inflammatory nodules. Increased lymphocytes were observed by cytology test in CSF, raising suspicion of possible viral encephalitis. Therefore, he was administered acyclovir until ruling out viral infection by pathogenetic testing. All the AE-related antibodies in the CSF obtained by lumbar puncture were non-reactive. Notably, using a cytometric bead array, laboratory findings revealed the presence of CASPR2 antibodies associated with AE in the serum. Hence, a diagnosis of AE was established. The patient was subsequently treated with glucocorticoids. His symptoms improved in response to this regimen. Upon discharge, the patient was advised to continue a regular course of therapy at home, with close monitoring and follow-up appointments.

Table 1 The laboratory test results upon the second admission of this patient

Laboratory test	Normal range	Value
CBC		
hemoglobin, g/L	115–150	123
white blood cell, /L	3.5–9.5*10^9	9.17
platelet, /L	100–300*10^9	365
Biochemistry		
protein, g/dL	65.0–85.0	40.9
albumin, g/dL	40.0–55.0	21.8
urea, mmol/L	2.6–7.5	2.4
creatinine, μmol/L	48–79	45
uric acid, mmol/L	160–380	60
e-GFR, (ml/min/1.73m^2)		121.1
Electrolytes		
kalium, mmol/L	3.5–5.3	3.89
sodium, mmol/L	137–147	135.5
chlorine, mmol/L	99–110	102
Urine sediment		
red blood cell, /uL	0–11	3
white blood cell, /uL	0–11	1
epithelial cell, /uL	0–6	2
cast, /uL	0–2	2
bacteria, /uL	0–30	5
Immune tests		
IgG, g/L	8.6–17.4	4.2
IgA, g/L	1-4.2	1.25
IgM, g/L	0.3–2.2	1.06
C3, g/L	0.7–1.4	1.36
C4, g/L	0.1–0.4	0.533
hs-CRP	< 7.44	28.9

Abbreviations CBC, complete blood count; e-GFR, estimated-glomerular filtration rate; Ig, immunoglobin; C, complement component; hs-CRP, hypersensitive C-reactive protein

Second admission

Despite adherence to the prescribed therapeutic regimen post-discharge, the patient experienced a recurrence of symptoms after 5 days. He was reassessed for AE in the emergency department and subsequently admitted for the second time. A thorough neurological examination yielded no clinically significant findings. The laboratory test results upon the second admission of this patient are shown in Table 1. Serological testing revealed the presence of LGl1 antibodies in the serum but not in the CSF. In the CSF, no nucleated cells were found, microprotein was 0.43 g / L (normal range 0.15–0.45 g/L), and the antibody of tuberculosis was negative. In light of the previous identification of CASPR2 antibodies, a diagnosis of AE with dual positivity for antibodies was made. Therefore, we treated him with 50 mg of prednisone to mitigate autoimmune reactions, along with other supportive measures. This intervention contributed to a marked improvement in his neuropsychiatric disorders.

Interestingly, during the treatment of anti-AE, two newly discovered pivotal findings related to other diseases confused us and prompted an in-depth investigation of the potential shared etiology. First, abdominal distention and symmetrical pitting edema in both lower limbs were found on regular visits. Moreover, a decrease in the serum albumin concentration to 19.2 g/L, with urinalysis indicating a 24-hour urine protein excretion of 11.76 g/L, a protein-creatinine ratio of 1.815 g/mmol Cr, and an albumin−creatinine ratio of 11,886.6 mg/g, led to an additional diagnosis of NS. In addition, the patient reported experiencing generalized itching. On physical examination, multiple scratch marks and areas of hyperpigmentation were present, yet the dermatographia test was negative. A dermatologist diagnosed him with pruritus. In addition, despite the initial treatment, incomplete relief of his complaints prompted us to further explore other potential causes.

He was then transferred to the nephrology department for further evaluation. Renal biopsy revealed

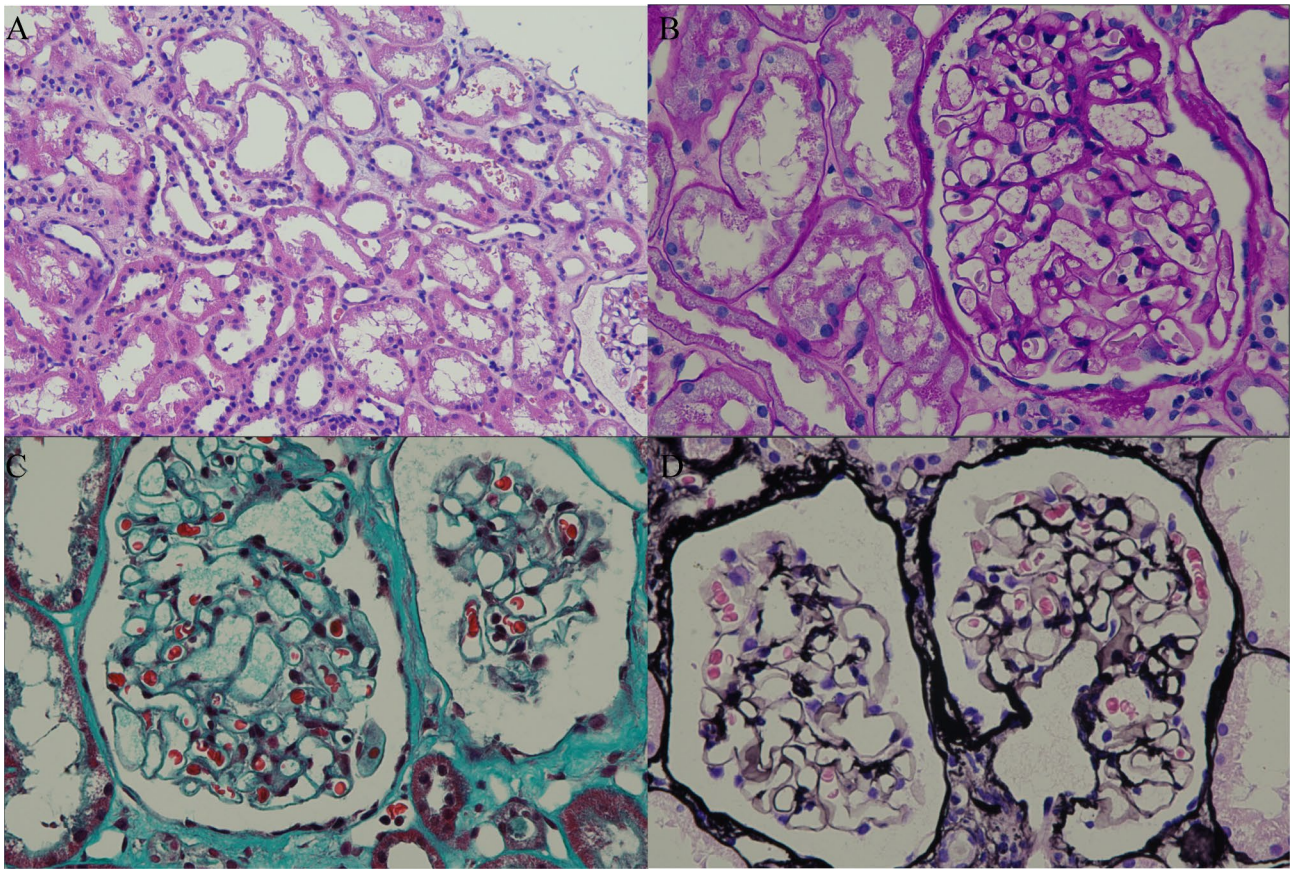

Fig. 1 Glomeruli under microscope of renal biopsy tissue. Panel **A**: Hematoxylin eosin staining (200 ×); Panel **B**: Periodic acid-Schiff staining (400×); Panel **C**: Masson staining (400×); Panel **D**: Periodic acid-silver methenamine staining (400×)

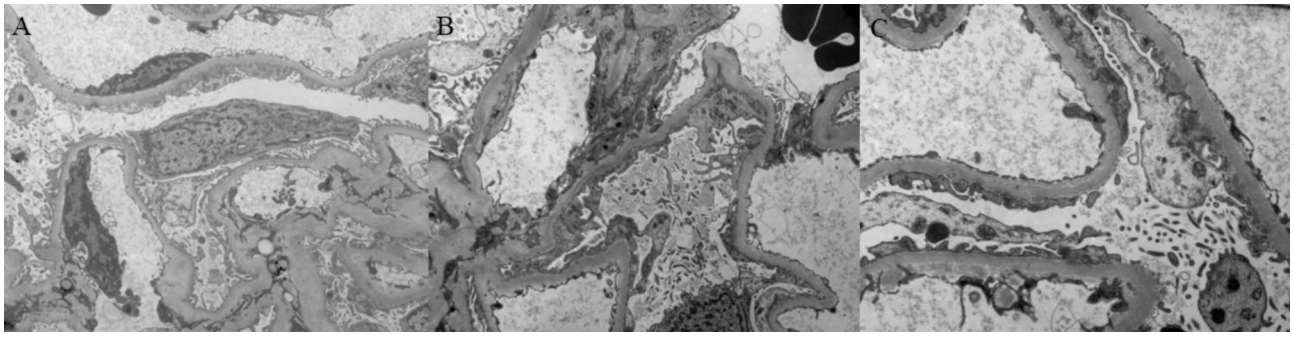

Fig. 2 Figure 2. Glomeruli under electron microscope of renal biopsy tissue. Panel A: Segmental subepithelial deposits typical of MN and podocyte effacement by electron microscope (2,500 ×); Panel B: 3,000×; Panel C: 5,000×.

membranous nephropathy (type I) with no detectable serum anti-phospholipase A2 receptor antibodies (anti-PLA2R antibodies). Microscopic examination revealed 14 glomeruli with mild mesangial hyperplasia, segmental vacuolar degeneration of the basement membrane, and signs of renal tubular atrophy and moderate epithelial cell degeneration (Fig. 1). The immunofluorescence (IF) demonstrated moderate immunoglobin (Ig) G positivity along the glomerular basement membrane (GBM) in four glomeruli, with mild positivity for IgM, complement component (C) 3, C4, and C1q. Regarding the electron microscopy findings, segmental subepithelial deposits typical of MN and podocyte effacement were present, which may represent early or evolving MN (Fig. 2). The results of renal biopsy were consistent with the pathological diagnosis of type I MN. Given the patient's multisystem symptoms, a comprehensive evaluation for autoimmune disorders was undertaken during hospitalization. Tests for antinuclear antibodies (ANA), anti-double-stranded DNA (dsDNA) antibodies, extractable

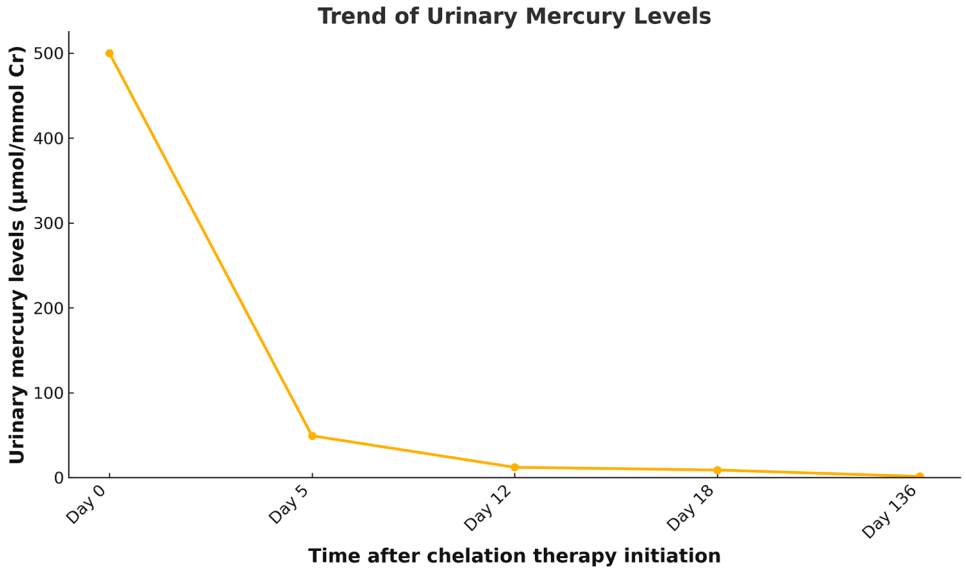

Fig. 3 The trend of urinary mercury levels

nuclear antigens (ENA), and anti-neutrophil cytoplasmic antibodies (ANCA) returned negative results, effectively excluding primary autoimmune conditions such as systemic lupus erythematosus (SLE). For another, severe multisystem diseases in the context of immune disorders made us consider the possibility of heavy metal poisoning. Surprisingly, a significant mercury concentration of >500 μmol/mmol Cr (normal range: 0–2 μmol/mmol Cr) was detected in the spot urine sample by inductively coupled plasma mass spectrometry (ICP-MS) [1]. Hence, we conducted an in-depth history inquiry and the patient recalled that he broke a thermometer in his bedroom but did not clear the spilled mercury four months before developing symptoms. Without other explicit history of heavy metal exposure, we hypothesized that his neuropsychiatric manifestations, albuminuria, and subsequent pruritus were potentially attributable to mercury poisoning, which suggested a complex interplay between mercury intoxication and autoimmune dysregulation. The patient was administered immunosuppressive therapy with prednisone to curtail the hyperactive immune response. In light of the hypoalbuminemia and the associated hypercoagulable status, he was administered Irbesartan 75 mg daily to relieve proteinuria and given low-molecular-weight heparin 4,000IU daily for anticoagulation. Furthermore, pregabalin was added to mitigate sensory abnormalities, and ebastine was prescribed for allergic reactions. Mercury displacement therapy with sodium dimercaptopropane sulfonate (DMPS) and tiopronin was initiated to inhibit the progression of poisoning. After 18 days of chelation therapy, the mercury concentration in the urine decreased to 9.0 μmol/mmol Cr, and the patient reported no discomfort. Hence, he was discharged from the hospital and continued prednisone, DMPS and tiopronin treatment. At the regular outpatient visit four months after discharge, the patient was negative for mercury and protein according to the urine analysis and without any discomfort. The trend of urinary mercury levels is visualized in Fig. 3.

Figure 2. Glomeruli under electron microscope of renal biopsy tissue. Panel A: Segmental subepithelial deposits typical of MN and podocyte effacement byBY electron microscope (200 ×); Panel B: 400×; Panel C: 600×.

Discussion

The patient, who had been hospitalized twice at our facility due to neuropsychiatric symptoms, was diagnosed with AE due to the presence of anti-AE antibodies. However, the anti-AE therapeutic outcome was not satisfactory. During the second hospitalization, another antibody associated with AE was also detected, confirming the diagnosis of AE. Concurrently, the patient exhibited significant proteinuria and severe hypoalbuminemia, suggesting the consideration of NS, which was further substantiated by renal biopsy for evolving MN. Multisystem involvement against a backdrop of immune dysregulation prompted an in-depth investigation into the underlying etiology. A markedly elevated mercury level was detected in the urine, which was a known potential cause of immune dysregulation [2]. Therefore, we proactively initiated chelation therapy for mercury intoxication on the basis of supportive immunosuppressive symptomatic treatments. After 18 days, there was a significant improvement in the patient's urinary mercury, urinary protein and neurological symptoms, which supports the diagnosis of mercury poisoning-associated AE and MN.

Mercury and its components are global health threats, ranking among the top 10 chemicals affecting the public

according to the World Health Organization [3]. Genetic background and mercury exposure both contribute to the occurrence of mercury poisoning [4]. Minamata disease in Japan and large-scale poisoning by methylmercury in Iraq have raised concerns about mercury poisoning-related impairments in human health [5]. The urinary mercury levels in 76.9% of the Chinese general public were below the WHO recommended value (4.0 μg/L) [6], and 92.3% were lower than the reference value (10.0 μg/L) set by the Chinese health authority [7]. There are diverse source-exposure scenarios with distinctive regional characteristics, such as amalgams, contaminated sites, cosmetics, electronic waste, and traditional medicine [3, 8]. This case highlights the need for clinicians to maintain vigilance regarding patients even in the absence of a clear history of occupational mercury exposure. Environmental contaminants increase their risk of mercury exposure, a factor that is often overlooked.

Mercury exists in different forms, including elemental, inorganic, and organic mercury, each with distinct physicochemical properties and toxicity profiles [9, 10]. In non-occupationally exposed populations, elemental mercury is primarily derived from dental amalgam and is excreted through feces and urine. The mercury vapor is often absorbed through the respiratory tract and impairs the kidney, respiratory, cardiovascular, neuromuscular, and nervous systems. Animal studies using rat models have demonstrated a dose-dependent effect of mercury level on renal cell apoptosis [11, 12]. In this case, the limited mercury exposure from a broken thermometer likely resulted in insufficient inhalation to cause significant pulmonary toxicity. Additionally, the kidneys and nervous system are more sensitive to mercury's toxic effects, potentially explaining the absence of lung involvement. Methylmercury is predominantly found in fish, whereas inorganic mercury typically originates from non-fish food sources. Gastrointestinal tract, kidney, and neuromuscular and nervous systems are usually injured by inorganic mercury exposure [13]. After entering the human body, different mercury forms can interconvert. For instance, vapor mercury is inhaled into the lungs, where it comes into circulation and rapidly being oxidized into Hg^{2+} by catalase enzyme, resulting to the targeted organs damaged [14, 15].

The molecular and cellular mechanisms underlying mercury poisoning is not fully understood. It has been proposed that multiple mechanisms contribute to mercury toxicity, including disturbance of regulating intracellular Ca^{2+} homeostasis, cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter release, DNA methylation, and overactivation of N-methyl-D-aspartate (NMDA) [14]. Mercury-induced autoimmunity and inflammation have been demonstrated in human and animal models [16]. In guinea pigs, rats, rabbits, and humans, mercuric chloride caused lymphoproliferation [17], which might further elicit the reaction of type 2 helper CD^{4+} T cells [18–20]. They present with various symptoms that are influenced by dose, exposure duration, strain, and genes [21–24]. In the mercury poisoning model, this autoimmunity is attributed to the classical T-dependent humoral immune response, generating anti-laminin antibodies which interact with the GBM, further leading to development of autoimmune glomerulonephritis [23, 25, 26]. In addition, deposits of IgG, IgM, and C3 have been observed along the GBM of rats after exposure to mercury for 2 years, accompanied with fibrotic changes in some glomeruli [27]. Epidemiological studies have also reported correlations between mercury exposure and autoimmune antibodies, such as antinuclear antibodies [28], multiple neural and nonneural IgM antibodies [29], and antifibrillarin autoantibodies, in distinct populations [30]. The prolonged presence of mercury causes chronic tissue damage and inflammation, leading to ectopic lymphoid structures [16, 31]. According to a cross-sectional study from the National Health and Nutrition Examination Survey (NHANES), methylmercury exposure might predict future autoimmune disease among reproductive-aged females [32].

Excessive mercury exposure can lead to multi-organ dysfunction. A retrospective study conducted in China from 2014 to 2019 reported that chronic mercury poisoning is systemic and occurs most often in the nervous system (50.3%) and kidneys (16.4%), followed by the respiratory system (8.0%) [8]. Additionally, it can also damage the cardiovascular, gastrointestinal, skin, ophthalmic and visual systems [33, 34]. However, reports of the typical behavior of multiple systems in one patient are rare [34]. This patient was highly representative due to a clear history of mercury exposure combined with neurological, renal, and skin lesions.

Recent retrospective studies revealed that kidney impairments were common manifestations in mercury poisoning populations, some of whom only exhibited proteinuria and increased urinary mercury concentrations [35]. A literature review summarized 26 patients who underwent kidney biopsy resulting from mercury poisoning-induced renal repair and reported glomerular disease in 21 patients. Among these patients, membranous glomerulonephritis accounted for the majority (15 patients), followed by minimal change disease in 4 patients [36]. Another study enrolled 41 mercury-associated NS patients, among whom 35 underwent renal biopsy. Eighteen (51.43%) patients had membranous glomerulonephritis, 13 (37.14%) had minimal changes, and the remaining 4 (11.43%) patients had mesangial proliferative glomerulonephritis and mesangial proliferative IgA nephropathy [35]. In a cohort enrolling 288 patients with mercury poisoning, 39 underwent renal biopsy, of which

20 (51.28%) presented with MN [8]. Similarly, the patient in this case also presented with large amount proteinuria and membranous glomerulonephritis, which echoes mercury poisoning. Previous reports of immune-related neurological disorders due to mercury poisoning are not uncommon. Compared with chronic mercury poisoning, acute mercury poisoning seems to be more threatening and has a worse prognosis. An enigmatic 23-year-old patient with acute mercury poisoning without a clear intoxication source presented with progressive neuronal deterioration, as well as immune and hemostatic system dysfunction. The patient eventually developed pale syndrome or a persistent vegetative state [37]. Another patient complained of progressive fatigue and limb pain for more than 4 months on admission. Mercury intoxication caused by cosmetic skin cream was suspected after misdiagnosis as a vertebral body disease [38]. In patients with neuropsychiatric symptoms as the chief complaint after mercury exposure, immune-related nervous system antibodies can often be positive. Li et al. found positive serum LGI1 and CASPR2 antibodies in an immune-associated neuromyotonia syndrome patient, which was highly consistent with the antibody results of our patient [39]. A report of 23 patients with mercury toxicity following unauthorized Siddha medicine intake also detected serum voltage-gated potassium channel-CASPR2 antibodies [27]. Therefore, we recommend that patients who present with neuropsychiatric symptoms and test positive for these two antibodies should be screened for mercury poisoning. Although there have been some cases of kidney and neurological impairments associated with mercury poisoning, concurrent involvement of multisystem has rarely been reported.

The thresholds for toxicity vary depending on the organ involved. Generally, acute toxic effects are typically observed at urinary mercury levels of 100 μg/L or blood mercury levels of 50 μg/L. For the kidney, mild proteinuria and enzymuria can be detectable at urine levels of >5–10 μg/g creatinine or above. The threshold for clear toxicity may be 35 μg/g creatinine [13]. In a Chinese cohort reporting the urinary mercury level of patients with mercury poisoning, patients with peripheral neuropathy had a median mercury concentration of 9.5 μg/L while patients with NS had a median urinary mercury level of 20.9 μg/L [8]. Another study enrolled patients with a chronic mercury exposure history reported the mercury concentration was 33.06 μmol/mmol Cr for patients with kidney damage, which was significantly higher than the 16.03 μmol/mmol Cr observed in patients without renal impairment [35].

Caza proposed that the diagnosis of mercury-associated MN is primarily based on clinical suspicion and often supported by measurements of serum and urine mercury levels, as well as histopathologic features on biopsy [41]. In this case, renal biopsy revealed deposits of IgG, IgM, C3, C4, and C1q, supporting the diagnosis of MN. Serum PLA2R was negative, effectively differentiating mercury-associated MN from primary MN, as has been observed in all reported cases of mercury-induced kidney injury [8]. We have screened potential etiologies for secondary MN such as malignancy and autoimmune diseases, but no positive findings were detected. Previous studies have highlighted differences in immune deposit subtypes between primary and mercury-associated MN. IgG4 is often predominant in primary MN, whereas IgG1 is the main immune deposit in mercury-related MN, a distinction that provides significant diagnostic support [42]. However, some examinations have not been performed for this patient, including pivotal markers like PLA2R, NELL-1, Exostosin, and THSD7A, and the IgG subtype tests in renal biopsy. In a Chinese cohort with a mercury exposure history, patients with NS had a median blood mercury content of 16.70 μg/L [8]. Another report described a 73-year-old male with chronic mercury poisoning presenting with NS, abdominal pain, and neuropsychiatric symptoms, who had a blood mercury level of 24.7 μg/L (reference: <2.5 μg/L) and a urinary mercury level of 33.4 μg/L (reference: <15 μg/L) [34]. Considering the patient's financial constraints and the fact that mercury concentrations in urine are more stable, mercury concentrations in blood were not measured. Taken together, we speculated that in this context of harmful immune activation caused by mercury, AE, NA and dermatitis occurred in the patient.

Increasing evidence suggests that chelation therapy can be safely utilized for the treatment of heavy metal intoxication. Since mercury is primarily excreted via the kidneys, renal tolerance during mercury elimination must be carefully monitored. Intermittent administration of chelating agents is often necessary to avoid excessive mercury excretion, which could exacerbate renal injury [35, 43]. Ideal chelating agents have a relatively high affinity for mercury and can be excreted from the body without interactions with beneficial bodily metals. A 38-year-old male received DMPS combined with hemodialysis after suffering from acute kidney injury due to a hazardous dose of a HgCl2-solution. He finally fully recovered after almost eight-week DMPS treatment [44]. Another study evaluated the efficacy of dimercaptosuccinic acid (DMSA) in reducing blood mercury levels among 767 children with mercury exposure. After three courses of treatment, the adjusted mean blood mercury concentration in the DMSA group decreased by 17%, compared to the placebo group [45]. In our case, chelation therapy was initiated after a multidisciplinary discussion, considering the patient's multisystem symptoms, such as nephrotic syndrome and neurological disorders, strongly associated with mercury exposure. We utilized DMPS to clear

mercury, which was more effective at removing deposited mercury from the kidneys and had fewer side effects than dimercaprol [46, 47]. As shown in Fig. 3, urinary mercury concentrations declined markedly during the early phase of chelation therapy, followed by a gradual decrease until normalization. This pattern aligns with trends observed in previous studies [35, 48].

However, we acknowledged that this case report has some limitations. The causal relationship between mercury exposure and autoimmune dysregulation remains uncertain, as other contributing factors cannot be ruled out. Additionally, the patient's improvement may be attributed to a combination of treatments rather than mercury chelation alone. Further studies are needed to elucidate the mechanisms linking heavy metal exposure and autoimmune disorders.

Conclusion

Patients with mercury poisoning are often initially referred to neurology, nephrology, or gastroenterology departments due to multisystem involvement, leading to potential misdiagnoses and symptomatic treatment. We report a case of concurrent AE and MN in a patient with a history of mercury exposure, whose neurological and renal symptoms improved following mercury chelation and immunosuppressive therapy. This case underscores the importance of considering heavy metal intoxication in patients with unexplained or refractory autoimmune-related conditions. While treatment strategies for mercury poisoning are established, further research is needed to clarify its role in immune dysregulation and guide optimal management.

Abbreviations

AE	Autoimmune encephalitis
MN	Membranous nephropathy
CSF	Cerebrospinal fluid
NS	Nephrotic syndrome
MN	Membranous nephropathy
MRI	Magnetic resonance imaging
Ig	Immunoglobin
GBM	Glomerular basement membrane
C	Complement component
ANA	Antinuclear antibodies
dsDNA	Anti-double-stranded DNA
ENA	Extractable nuclear antigens
ANCA	Anti-neutrophil cytoplasmic antibodies
SLE	Lupus erythematosus
ICP-MS	Inductively coupled plasma mass spectrometry
DMPS	Dimercaptopropane sulfonate
NMDA	N-methyl-D-aspartate
NHANES	National Health and Nutrition Examination Survey

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None.

Author contributions

YZ and CL: draft preparation, conceptualization, writing; YH, WW, and XH: conceptualization; JY and YZ: revision. All co-authors were involved in patient care and participated in manuscript revision.

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Data availability

Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate

Institutional Review Board approval was not required as this was a case report. Informed consent to report the case was obtained from the patient.

Consent for publication

The patients have given written informed consent for their personal or clinical details along with any identifying images to be published in this study.

Competing interests

The authors declare no competing interests.

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