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Case Report

Mercury exposure mimicking systemic lupus erythematosus in a thirteen-year-old girl

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ABSTRACT

Background. The clinical presentation of mercury (Hg) intoxication may mimic rheumatic diseases. Hg exposure is associated with systemic lupus erythematosus (SLE)-like disease in genetically susceptible rodents and Hg is among the environmental factors in the development of SLE in humans. Herein, we presented a case with clinical and immunological features suggestive of SLE but diagnosed with Hg intoxication.

Case. A thirteen-year-old female with myalgia, weight loss, hypertension and proteinuria was referred to our clinic for the evaluation of possible SLE. Physical examination of the patient was unremarkable except for a cachectic appearance and hypertension, laboratory investigation revealed positive anti-nuclear antibody, dsDNA antibody and hypocomplementemia with nephrotic range proteinuria. Inquiry for toxic exposures revealed a continuous exposure to an unknown silverly shiny liquid for a month which was thought to be Hg. Due to the fulfillment of Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE, a percutaneous kidney biopsy was performed whether proteinuria resulted because of the Hg exposure or flare of lupus nephritis. Blood and 24-hour urine Hg levels were high, and no findings associated with SLE were observed in the examination of the kidney biopsy. The patient was diagnosed with Hg intoxication and, clinical and laboratory findings, including hypocomplementemia, positive ANA and anti-dsDNA antibody, improved with chelation therapy. Also, no findings associated with SLE were observed in the follow-up of the patient.

Conclusions. In addition to the toxic effects, Hg exposure may cause autoimmune features. As far as we know, this is the first-time Hg exposure was associated with hypocomplementemia and anti-dsDNA antibody in a patient. Also, this case highlights the inconvenience of the use of classification criteria for diagnostic purposes.

Key words: autoimmunity, mercury, nephritis, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by autoantibody development with marked heterogeneity between presentations. SLE develops through the effects of epigenetic, immunomodulatory, hormonal and environmental factors in genetically susceptible individuals.[1] Air pollution, ultraviolet light exposure, infections, vaccinations, pesticides, and heavy metals are among the several possible environmental factors.[2]

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Mercury (Hg) is a heavy metal with a shiny white-silver appearance which has toxic properties affecting both humans and the environment. Gold mining, dental amalgams, thermometers, and other measuring devices are sources of elemental (metallic) Hg exposure and the primary route of exposure is through inhalation. Elemental Hg has toxic effects on the nervous system, lungs, kidneys, and skin.[3]

Besides toxic effects, Hg may induce autoimmunity. It has been shown that Hg exposure is associated with the development of anti-nucleolar antibodies and lupus-like autoimmune disease in genetically susceptible rodents. Also, Hg triggers the production of

pro-inflammatory mediators in humans. It might have a role in development of several autoimmune diseases like scleroderma, multiple sclerosis, membranous nephropathy and SLE.[4]

Herein, we report a pediatric patient with Hg poisoning, referred to our department with a possible diagnosis of SLE. The relationship between Hg and autoimmunity has also been briefly reviewed.

Case Report

A thirteen-year-old female with myalgia, weight loss, hypertension and proteinuria was referred to our clinic for the evaluation of a possible rheumatic disease. She had developed myalgia about a month ago, which got worse over time and had lost five kilograms in that process. She had neither arthritis nor morning stiffness, and her pain was not responsive to non-steroid anti-inflammatory drugs or gabapentin. She suffered from a rash on her fingers at the time of the occurrence of myalgia but this resolved spontaneously in two days. She had no other complaints, including fever, photosensitivity, malar rash, oral/nasal ulcers, alopecia, and Raynaud's phenomenon. Her family history was negative for rheumatic diseases. Her weight was 35 kg (< 3rd centile) with a height of 162 cm (50th-75th centiles). Her blood pressure was high (150/100 mmHg) with mild tachycardia (110/min). Respiratory rate, body temperature and oxygen saturation were within normal limits. Her physical examination was unremarkable except for a cachexic appearance and generalized myalgia. Laboratory findings, including hemoglobin, lymphocyte, leukocyte, and thrombocyte indices, were within normal ranges and acute phase reactants were not elevated. Urinalysis revealed a proteinuria of 100 mg/dL with a density of 1.010 without hematuria. Despite having nephrotic range glomerular proteinuria (44 mg/m^2/hr), serum albumin (38 g/L) and creatinine (0.38 mg/dL) levels were within normal limits. Serum level of complement C3 was low (0.64 g/L) with a normal complement C4 (0,1 g/L) level. Anti-nuclear antibody (ANA) was positive, with a titer of 1/320 and stained as nucleolar pattern and anti-double stranded DNA (dsDNA) antibody levels were high (260 IU/mL, normal range < 100 IU/mL) with a normal screening result for extractable nuclear antigen antibodies. She fulfilled the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) classification criteria for SLE[5] with proteinuria as a clinical criterion and hypocomplementemia, positive ANA and anti-dsDNA antibody as laboratory criteria. A calcium channel blocker and angiotensin converting enzyme inhibitor were required to control her hypertension. She was started on prednisolone (40 mg/day) and a percutaneous kidney biopsy was planned for possible lupus nephritis. On the second day of admission, we found out that her 16 year old brother was also admitted to the hospital for myalgia in his legs. Due to the presence of myalgia in two individuals from the same household, a more detailed inquiry for toxic exposures was made. It was found out that she had been playing with an unknown silvery shiny liquid which was thought to be Hg and kept it under her pillow and had slept with it for over a month. Hg analysis in blood and urine were studied for suspected Hg intoxication. Percutaneous kidney biopsy was performed to identify whether nephrotic range proteinuria resulted from Hg exposure or a flare of lupus nephritis. Light microscopic changes were consistent with acute tubular necrosis and membranous nephropathy, but no immune complex deposition was observed in immunofluorescence microscopy. Hg levels in 24-hour urine were high (520 μg/L, normal range < 10 μg/L) and all the findings in the renal biopsy were attributed to Hg intoxication. Chelation therapy with dimercaptosuccinic acid (DMSA) was initiated with the tapering of prednisolone therapy. DMSA was given at a dose of 30 mg/kg per day for five days followed by a dose of 20 mg/kg/day for 14 days. Due to the high urinary Hg levels (242 μg/L) two weeks after the

first course of treatment, chelation therapy was continued with two cycles of treatment each lasting 7 days at a dose of 20 mg/kg/day. Her brother was also admitted to another institution with a diagnosis of Hg poisoning with mild clinical findings. Her mother, who shared the same bed with our patient, also presented with myalgia and proteinuria (1.9 gr/day). She was also diagnosed with Hg poisoning with elevated urinary Hg level (215 μg/L) and her biopsy findings were consistent with membranous glomerulonephritis. Myalgia in our patient recovered in two weeks, hypertension resolved in the first month of treatment, and she started to gain weight at the end of the first month. Complement levels also normalized with negative ANA and anti-dsDNA antibody in a month after chelation therapy. It took two months of chelation therapy to achieve an acceptable range of urinary Hg level (<20 μg/L). Despite the resolution of hypertension, angiotensin converting enzyme inhibitor therapy was continued for its anti-proteinuric and renoprotective effects. Proteinuria gradually decreased and resolved completely at the sixth month follow up and no complaints or findings associated with SLE were observed.

The patient and her legal guardian gave verbal and written consent for publishing this case report.

Discussion

Diagnosis of SLE should be kept in mind, especially in patients with multisystemic autoimmune disease involvement, but no gold standard test exists for its diagnosis. Constitutional symptoms, myalgia, and proteinuria along with positive ANA, anti-dsDNA antibody and hypocomplementemia, in our patient were consistent with SLE. SLICC 2012 criteria could aid referral or consultation to pediatric rheumatology but it is important to remember that these criteria were developed for classification and not for diagnosis.[6] As seen in our case, non-rheumatic diseases may mimic SLE and even fulfill SLICC criteria.

Even though our case was not SLE, Hg exposure is regarded as an environmental factor in the development of the disease.[2] In a study with 265 SLE patients, self-reported Hg exposure was associated with SLE development with an odds ratio of 3.6.[7] Additionally, Dahlgren et al.[8] reported a 20 time increased risk for SLE in a population living in an oil waste site, which had higher ambient air Hg levels.[8] In an experimental study, methyl-Hg exposure of peripheral blood monocytes resulted in an increased pro-inflammatory response in patients with SLE when compared with healthy controls.[9] But, in a study with 53 SLE patients, Hg exposure was not associated with increased disease activity or damage.[10] Besides being an environmental factor for SLE development, Hg exposure was linked with an increased prevalence of ANA and anti-nucleolar antibodies in selected populations.[11] Also in a study with gold miners, exposure to Hg was associated with increased concentrations of pro-inflammatory cytokines besides the increased prevalence of ANA.[12] Our case had low levels of C3 and positive anti-dsDNA besides positive ANA. As far as we know, there is no report of hypocomplementemia and positive anti-dsDNA antibody in association with Hg exposure in the literature. Owing to the recovery of hypocomplementemia and disappearance of dsDNA antibody on chelation therapy, concomitant SLE was ruled out. Because of the immune effects of Hg exposure, it was thought that these findings might be secondary to Hg exposure.

In animals expressing H-2^s haplotype, Hg exposure is associated with systemic autoimmunity. These animals are susceptible to autoimmunity only with an environmental factor. Anti-nuclear, anti-glomerular basement membrane, anti-dsDNA and anti-fibrillarin antibodies were among the autoantibodies observed in animal models of Hg exposure and these antibodies are also known to be associated with human diseases.[10] Hg exposure causes oxidative stress and induces alterations in mitochondrial function resulting in reactive oxygen species production and apoptotic

signal activation in human T lymphocytes.[13] Mitochondrial dysfunction and associated aberrant lymphocyte behavior, increased apoptosis and redox imbalance might also contribute to the immunopathology of SLE.[14]

Elemental Hg is highly lipophilic and rapidly distributed throughout the body, and exposure may result from several reasons. However, elemental Hg exposure is rare in most developed countries and occurs accidentally.[3] Our patient found a bottle that was filled with Hg in a schoolyard. Thus, we thought that exposure was welded by laboratory equipment. Proper storage and disposal of such laboratory equipment are important to avoid accidental exposures.

Proximal tubules are the most sensitive part of the kidney to the toxic effects of Hg exposure. With higher concentration of exposure, more distal parts of the nephrons might also be affected. Accumulation of Hg in proximal tubular cells induces oxidative stress, which might result in acute tubular necrosis.[15] Hg exposure is also associated with glomerular changes. It was suggested that high concentrations of Hg directly damage the podocytes and causes minimal change disease while long-standing exposure to low concentration of Hg may cause membranous glomerulonephritis through an immune mechanism.[16] A summary of the toxic and immunologic effects of Hg exposure is shown in Fig. 1. In most of the in-vitro studies investigating the effects of Hg exposure on the immune system, higher Hg concentrations than expected in the general population were used.[10] Therefore, the results of these studies may not reflect the true effects of Hg exposure.

Symptoms and findings of Hg exposure like pain, weight loss, hypertension and proteinuria could be seen in association with systemic rheumatic diseases and the occurrence of these findings may cause the referral to pediatric rheumatology like our case. Two case series from Turkey reported a total of 12 pediatric cases with Hg poisoning, referred to pediatric rheumatology. In those studies, weight loss and extremity pain were seen in eight and nine out of 12 patients, respectively. Interestingly, none of those cases had positive ANA.[17,18] Our case had hypocomplementemia and positive dsDNA antibody together with ANA positivity. Continuous long-term exposure to Hg over a month could explain those findings, which was the major difference in our patient than the reported cases above.

In conclusion, symptoms and findings of Hg poisoning may mimic rheumatic diseases. Hg may induce autoimmunity and cause autoantibody production; thus misdiagnosis is possible, especially when classification criteria

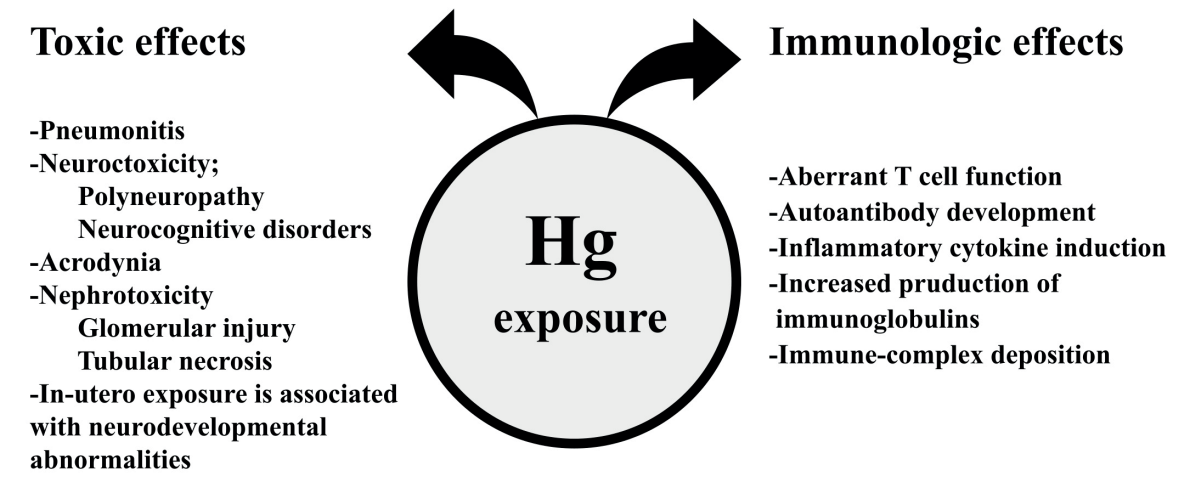

Fig. 1. Summary of toxic and immunologic effects of mercury (Hg) exposure.[3,10]

are used for diagnostic purposes. To the best of our knowledge, this is the first case of Hg intoxication mimicking SLE that even fulfilled the SLICC classification criteria. This case also highlights the importance of investigation for toxic exposures, when more than one person in the same household present with similar symptoms.

Ethical approval

The patient and her legal guardian gave verbal and written consent for publishing of this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HK, OB; data collection: HK; analysis and interpretation of results: HK, OB, MK; draft manuscript preparation: HK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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