Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

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Date(s) and place (hospital) of patient encounter: Princess Margaret Hospital on 7th Nov, 2022
Date of report submission: 5th March, 2023

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: A case of mercury-associated nephrotic syndrome in a young lady

Case history:

A 45-year-old Filipino lady who worked as a domestic helper in Hong Kong and enjoyed good past health presented to the hospital in October, 2022 with a few days' history of bilateral lower limb swelling. She had no dyspnea or fever. Physical examination revealed bilateral pitting lower limb edema up to knees with no overlying erythema or wound. There was no tenderness or raised temperature on palpation. Systemic examination was otherwise unremarkable except for a fair complexion over her face. She was afebrile with an oxygen saturation of 97% on room air. Blood tests showed an unremarkable complete blood picture except haemoglobin of 17.1 g/dL. Renal function test showed normal findings of Creatinine 55umol/L with electrolytes in the normal range. There was hypoalbuminaemia with albumin <8g/L, while other components of the liver function test were unremarkable. Thyroid function test showed evidence of hypothyroidism with low free thyroxine 8.3 pmol/L and an elevated thyroid-stimulating hormone at 14.4 mIU/L. Chest radiograph was clear with no cardiomegaly.

Further workup for the hypoalbuminaemia showed urine protein creatinine ratio 15.60mg/mg and a 24-hour urine total protein 13.53g. Initial workup for nephrotic syndrome was largely unremarkable including a negative anti-nuclear antibody, rheumatoid factor, anti-neutrophil cytoplasmic antibody, and normal anti-glomerular basement membrane level. Anti-streptolysin O titre was less than 200 IU/ml. Immunoglobulin A (IgA) was 4.50 g/L (H), immunoglobulin G (IgG) 4.21 g/L (L) and immunoglobulin M (IgM) 0.98 g/L (N). Complement 3 (C3) was 1.87 g/L. Hepatitis B and C testing were negative. Glycated haemoglobin (HbA1c) was 5.6% while low-density lipoprotein (LDL) was elevated up to 13.0 mmol/L. Anti-thyroid antibodies were negative.

Further testing revealed that blood mercury level was elevated to 110 nmol/L (H; ref: ≤77). 24-hour urine mercury level was 923nmol/24 hour (H; ref: ≤50). Renal biopsy was done and light microscopy showed 30 glomeruli with no significant expansion of mesangium or cellularity, no deposits, spikes, tramline or crescents. Immunofluorescence study showed no significant IgA, IgG, IgM, C3, fibrinogen, or C1q deposits. On electron microscopy, podocytes showed diffuse fusion, there were scanty subepithelial deposits in the capillary loop and no mesangial deposits were found. Diagnosis of mercury-associated minimal change disease was made.

She was started on atorvastatin for her raised LDL, thyroxine supplement for hypothyroidism and given intravenous frusemide and albumin infusion. Hong Kong Poison Information Centre (HKPIC) was consulted and the patient was given 19 days course of Dimercaptosuccinic acid (DMSA) chelation therapy. On further questioning, the patient reported that she had been applying a whitening cream in the recent 3 months, otherwise no other source of mercury exposure could be elicited. She was discharged and given intravenous frusemide and albumin infusion on an out-patient basis.

She was followed up after completion of DMSA therapy. 24-hour urine mercury level was 78.7nmol/24hr, while 24 hours urine total protein was 2.98g – both of which were coming down and improving. [Table 1]

The whitening cream product being used by this patient was sent for testing and the mercury content was 26131 ug/g, which has exceeded the maximum permitted limit, and is in contravention of the Consumer Good Safety Ordinance (CGSO). Boxes of the whitening cream product was seized from the retailers and a woman was arrested for further investigation.

Discussion and literature review

Proteinuria or nephrotic syndrome is a commonly encountered clinical condition in our daily practice. Nephrotic range proteinuria is defined as greater than 3.5g of protein in a 24-hour urine collection, with other clinical features being hypoalbuminaemia, generalized edema, hyperlipidaemia, hypercoagulopathy and various other complications. Primary glomerular diseases causing nephrotic syndrome according to pathology with corresponding incidence include minimal change disease (33.3%), membranous nephropathy (23.6%), focal segmental glomerulosclerosis (3.2%), and membranoproliferative glomerulonephritis (1.6%). Systemic illnesses with secondary glomerular involvement include diabetes mellitus (5.8%), autoimmune disorders, for example lupus nephritis (12.8%), amyloidosis (2.5%), infections, malignancies, and exposure to various drugs and toxins. [1] Mercury-associated nephrotic syndrome, as in this case, is a clinical scenario which is less commonly encountered and may be missed if we as clinicians fail to elicit this part of the history.

Mercury can enter the human body via inhalation, ingestion and absorption through skin. Possible sources of mercury exposure in daily life include mining, ingestion or exposure to fish or shellfish, and manufacturing of different technical or medical instruments, for example thermometers, sphygmomanometers and dental fillings. Mercury is also present in consumer products, for example cosmetic products, batteries, and hair-dyes. [2, 3] Clinical manifestations depend on chronicity and concentration of mercury exposure. Acute exposure to high concentrations of mercury can result in symptoms of vomiting, diarrhea, dyspnoea or even life-threatening interstitial pneumonitis. Chronic exposure to low concentrations of mercury mainly results in renal and also central nervous system side effects such as tremor, insomnia, memory loss and depression. [2, 3, 4]

Nephrotoxicity from mercury commonly manifests as nephrotic syndrome or tubular injury. [3] Mechanism of glomerular injury is unclear, and current suggestions are that idiosyncratic reactions or an abnormal immune response to the heavy metal result in nephrotic syndrome. Individual susceptibility also contributes since some individuals with similar exposure to mercury remain asymptomatic and unaffected. [3, 5] Among cases presenting with nephrotic syndrome due to mercury poisoning, the most common renal pathology are minimal change disease (60%), membranous nephropathy (37.1%), and focal segmental

glomerular sclerosis as evidenced from previous case reports. [3, 5, 6, 8]. The first proven case of minimal change disease due to mercury exposure is described in 2006, [6] and from then on there has been increasing number of cases of nephrotic syndrome described in association with mercury poisoning due to use of cosmetic products. [5]

Diagnosis of mercury-induced nephrotic syndrome is confirmed by testing of mercury levels in body by either blood or 24-hour urine sample for mercury, and also spot or 24 hour-urine saving for demonstration of nephrotic range proteinuria. Renal biopsy is helpful to elicit the underlying renal pathology. However, we should be aware that patients may have elevated mercury levels in the body but remain asymptomatic, and the levels do not correlate well with clinical findings and degree of symptoms. Urine excretion is the major route of excretion for mercury, while it has a short half-life in blood. [5] Urine concentration of mercury is a good indicator of medium to long-term exposure, while blood concentration of mercury indicates recent exposure if any. [4, 5]

Chelator therapy should be administered to selected patients especially those with a high mercury concentration in the body and with corresponding symptoms attributed to mercury intoxication. [9] Nephrotic syndrome resulting from mercury intoxication is usually reversible after elimination of the responsible agent and majority of patients can achieve complete remission. However, the optimal duration and dosage of chelation therapy, and the role of adjunctive steroids remains unclear. [3, 5, 8] In a case series, up to 77.8% patients achieved complete remission after detoxification monotherapy, but addition of immunosuppressants did not shorten the remission time for patients presenting with mercury-associated minimal change disease. [8] As in our case, the patient’s proteinuria gradually improved after administration of DMSA without any other adjunctive therapy such as steroids or immunosuppressants – which may be the treatment of choice in other causes of nephrotic syndrome. Hence elucidating the appropriate history such that we can achieve the diagnosis of mercury-associated nephrotic syndrome is crucial in deciding the appropriate therapy.

In our case, the patient is a young lady who works as a domestic helper. Initial workup for proteinuria is negative, and she has no underlying diabetes mellitus or any other autoimmune features. Clinically, the patient’s skin complexion of her face looks lighter compared to other parts of her body, which led to the suspicion of possible whitening cream use. We should stay observant as a clue as little as

patient's skin complexion may point us to the correct diagnosis. It is also important to take an occupational and diet history especially when the cause of nephrotic syndrome is not immediately obvious to look for any suspicious exposure history. Other than hyperlipidaemia as a complication of nephrotic syndrome, the patient also had hypothyroidism, which is a known common feature of nephrotic syndrome. This is due to increased urinary excretion of thyroid hormones and also thyroxine-binding globulin, which subsequently leads to low thyroxine level and hypothyroidism. Mercury itself has also been proposed to cause thyroid disorders as it can trigger oxidative damage, genotoxicity and autoimmune reactions which can subsequently cause hypothyroidism, autoimmune thyroiditis and thyroid cancers. [10]

Mercury is a toxic heavy metal which can lead to disastrous health hazards, and global effort is made to gradually reduce products utilizing mercury as a component and also to reduce occupational exposure. The Minamata Convention is a global initiative to reduce mercury emissions to protect human health. [2] Mercury compounds are used in cosmetic preparations for their skin-lightening effect as it can inhibit melanin production. Mercury can then enter the body through skin absorption [4, 5] and is one of the ways through which the general public can be exposed to mercury. In the current era, cosmetic products are widely used among ladies of a large age range, while some of these beauty products may not have undergone proper testing. It is hence important to educate the general public and to warn consumers not to use beauty products with doubtful sources and unknown composition, so as to avoid the long-term side effects due to chronic exposure to mercury. The Mercury Control Ordinance aims to implement the Minamata Convention on Mercury in Hong Kong, which is a global initiative to reduce mercury exposure. The ordinance aims at regulating the export and import of products containing mercury in order to promote public health and to achieve a living environment safer to all of us.

Mercury intoxication, commonly due to use of skin-lightening cosmetics products in the current era, is one of the rarer causes of nephrotic syndrome. We as clinicians should stay highly vigilant and to elicit this piece of history especially in young or middle-aged ladies who present with nephrotic syndrome but with unremarkable initial workup for nephrotic syndrome. We should also be aware of associated features of nephrotic syndrome and mercury intoxication so we can screen for these symptoms and do appropriate workup.

Tables and figures (where applicable) (no more than two figures)

Table 1 – Investigation results – 24-hour urine mercury level, 24-hour urine protein

Date	3/11/2022	19/1/2023		
24-hour urine mercury level (Ref: ≤50)	923 nmol/24h	78.7 nmol/24h		
Date	31/10/2022	28/11/2022	12/12/2022	18/1/2023
24-hour urine protein (Ref: 0.05-0.1)	13.53 g/24h	9.87 g/24h	12.76 g/24h	2.98 g/24h

Reference (not more than 10)

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10. Pamphlett R, Doble PA, Bishop DP. Mercury in the human thyroid gland: Potential implications for thyroid cancer, autoimmune thyroiditis, and hypothyroidism. Freedman JH, editor. PLoS ONE. 2021 Feb 9;16(2):e0246748.

No of words in Case History and Discussion (excluding references): 1688

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

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