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Case Report

Heavy Metal Exposure in Alport Syndrome in an Adolescent: A Case Report

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ABSTRACT

Alport syndrome is an inherited glomerular disease characterized by hematuria, proteinuria, hypertension, progressive kidney failure, hearing loss, and ocular pathologies. It is caused by a mutation in *COL4A3*, *COL4A4*, or *COL4A5* genes. A lamellar or uniformly thinned glomerular basement membrane is a pathognomonic histologic appearance for Alport syndrome. Light microscopy shows nonspecific findings, including mesangial matrix expansion and hypercellularity. Renal tubules are other main components of the kidney and the major sites in response to injuries. They are vulnerable to various conditions, such as hypoxia, proteinuria, and nephrotoxic substances, including heavy metals, like lead and mercury. We demonstrated that a patient with asymptomatic Alport syndrome may have accelerated worsening of kidney functions due to occupational exposure to lead and mercury. Regarding the initial diagnosis with current clinical and laboratory findings in patients, it is noteworthy that there is always the possibility of another pathology, and additional investigations may be needed. Besides, when considering public health issues and the financial burden due to occupational diseases, we desired to draw attention to the importance and need to create safer work environments and make frequent inspections.

Keywords: Mercury, Lead, Alport syndrome, Kidney, Public health

Introduction

Alport syndrome is an inherited progressive form of glomerular disease that is often associated with sensorineural hearing loss and ocular abnormalities. The overall incidence in the general population is unknown, but it accounts for 3% of children with kidney failure [1]. There is a risk of environmental or occupational exposure to heavy metals for all age groups all over the world. This exposure causes many systemic morbidities and even mortality [2].

In this case report, deterioration in kidney functions after exposure to toxic substances in an undiagnosed adolescent with Alport syndrome was demonstrated.

Case Presentation

A 17-year-old boy was referred to our department for the assessment of elevated serum creatinine and proteinuria. He had complaints of nausea, vomiting, and weakness for five months. Past medical history was negative for any particular disease and family history was unremarkable. He had no previous urine analysis, but serum

creatinine was normal in a routine visit one year ago. Although he did not describe any recent drug use, the patient worked in a furniture workshop where he was exposed to intensely volatile scented paints. However, he had not been able to work for the last two months due to an augmentation of his complaints. On the day of admission, vital signs were as follows: Blood pressure (BP): 135/86 mmHg (96th and 98th percentiles for systolic and diastolic BP, respectively), pulse: 84/min, body temperature: 36.8°C, and respiratory rate: 18/min. Physical examination showed nearly normal growth with body weight of 61 kg (10-25th percentile), height of 164 cm (3-10th percentile) with completely normal systemic examinations, and no evidence of edema. Laboratory analysis showed a normal complete blood count; however, some abnormalities were found in kidney function tests with increased blood urea nitrogen and creatinine. Hyperuricemia was also noted. The estimated glomerular filtration rate (eGFR) was decreased. He also had metabolic acidosis. Ferritin level was normal but parathyroid hormone level was slightly increased.

Urinalysis was positive for glucose and blood. Dysmorphic red blood cells were detected with no red cell casts on microscopy. Urine culture was negative. Both tubular phosphate reabsorption and fractional sodium excretion were decreased. Spot urine calcium/creatinine ratio was normal. Daily urine output was normal whereas there was nephrotic range proteinuria. Ultrasonography showed kidneys with normal sizes (90×34 mm on the right and 108×35 mm on the left) but increased bilateral parenchymal echogenicity was found.

In the immunologic evaluation, serum complement levels were normal. Antinuclear antibody (ANA), antineutrophilic cytoplasmic antibody (ANCA), anti double stranded DNA (anti-dsDNA), and anti-glomerular basement membrane (anti-GBM) were all negative. Investigation for infectious markers revealed a negative throat culture for group A beta-hemolytic streptococci and normal anti-streptolysin O titer. Viral markers were also negative.

Considering the occupational exposure of the patient, toxic screening was performed for heavy metals. The mercury (Hg) levels were high in both urine and serum. Urine lead (Pb) levels were also high.

On the kidney biopsy, light microscopic evaluation revealed nine glomeruli with global glomerulosclerosis in two of them. Mild mesangial matrix increase was observed in the non-sclerotic glomeruli. Periglomerular fibrosis and ischemic collapse characterized by glomerular capillary folding were present in three glomeruli. The interstitium had an edematous appearance and was inflamed, especially in the parenchymal areas where global sclerotic glomeruli existed. The inflammatory infiltrate was mononuclear, with no eosinophils or polymorphonuclear leukocytes. There were fibrosis and atrophic tubular structures in the parenchyma where collapsed glomeruli were observed. Diffuse acute tubular injury characterized by cytoplasmic vacuoles, flattening of the epithelium, and nuclear loss was observed in the non-atrophic tubular epithelia. No staining was detected in the immunofluorescence examination. Electron microscopic evaluation of the biopsy material was unavailable. Biopsy images are shown in Figure 1.

The clinical findings of the patient were microscopic hematuria, nephrotic range proteinuria, and elevated serum creatinine. Besides, hypertension (HT) was noted, which necessitated treatment with an angiotensin-converting enzyme inhibitor (ACEi). These findings raised suspicion for glomerular disorders, including Alport syndrome. Examinations in terms of extrarenal manifestations of the disease showed bilateral mild sensorineural hearing loss. The ophthalmologic examination was normal. As kidney biopsy findings were not considered pathognomonic for Alport syndrome, nephrogenetic analysis was performed and c.1093G>A p.G365R hemizygous mutation in the *COL4A5* gene was detected.

Considering the medical history of the patient and the borderline elevation in the serum and/or urine toxic substance levels, he was evaluated by the department of occupational diseases. Since he had no toxic exposure for the last two months, no specific chelation therapy for intoxication was indicated. Thiamine and ascorbic acid were started for Pb intoxication, and N-acetyl cysteine (NAC) and vitamins C and E for Hg intoxication. During the follow-up period, heavy metals were unnoticeable in the blood and urine. Although urinary protein excretion decreased below the nephrotic range, serum creatinine was persistently high, and eGFR was consistent with stage 3 chronic kidney disease.

The laboratory values of the patient on admission and in the last follow-up visit six months after admission are shown in Table 1.

The follow-up of the patient continues jointly with the department of occupational diseases, department of eye diseases, and hearing department.

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Table 1. Laboratory results of the patient on admission and in the last follow-up visit six months after admission

Laboratory Tests		On Admission	Last Follow-up	Reference Values
Blood	Hemoglobin (g/dL)	14.6	13.6	13-17.1
	White blood cell (/uL)	6900	8400	4000-10000
	Neutrophil (/uL)	5000	5900	1500-7000
	Eosinophil (/uL)	100	100	<500
	Platelets (/uL)	211000	254000	150000-400000
	BUN (mg/dL)	50	29	5-18
	Creatinine (mg/dL)	1.81	1.98	0.26-0.77
	Uric acid (mg/dL)	10	6.2	3.5-7.2
	Albumin (g/dL)	3.8	3.9	3.5-5.2
	Calcium (mg/dL)	8.9	9.4	8.4-10.2
	Sodium (mmol/L)	141	139	136-146
	Potassium (mmol/L)	5.1	5.0	3.5-5.1
	Ferritin (ng/mL)	51	58	24-336
	PTH (pg/mL)	81	95	15-65
	pH	7.31	7.38	7.35-7.45
	pCO_2 (mmHg)	38.4	34.6	35-45
	HCO_3 (mmol/L)	19.1	21.7	22.0-30.0
	BE (mmol/L)	-1.7	-2.4	(-2)-(+2)
	aPTT (seconds)	20.8		20-32
	C3 (mg/dL)	86		79-152
	C4 (mg/dL)	30.7		16-38
	ANA	Neg		Neg
	Anti-dsDNA (IU/mL)	Neg		Neg
	c-ANCA	Neg		Neg
	p-ANCA	Neg		Neg
	Anti-GBM	Neg		Neg
	ASO (IU/mL)	44.4		0-200
Urine	pH	6	5.5	5.0-7.5
	Density	1019	1016	1005-1030
	Leukocyte esterase	Neg	Neg	Neg
	Nitrite	Neg	Neg	Neg
	Hb	+++	+++	Neg

Laboratory Tests		On Admission	Last Follow-up	Reference Values
Urine	Glucose	++	Neg	Neg
	Leukocyte (/HPF)	2	2	<5
	Erythrocyte (/HPF)	430	141	<5
	Protein (mg/day)	4555	905	<150
	Volume (mL/day)	2300	1300	
	TRP (%)	76	88	78-91
	FeNa (%)	0.3	1	<1
	Spot Ca/Cre (mg/mg)	0.11	0.16	<0.2
Heavy metals	Lead (µg/L) (urine)	9.05	3.4	0-5
	Lead (µg/L) (blood)	29.3	18.6	0-49
	Mercury (µg/L) (urine)	12.8	2.1	0-5
	Mercury (µg/L) (blood)	10.6	1.8	0-10

Abbreviations: BUN: Blood urea nitrogen; PTH: Parathormone; BE: Base excess; aPTT: Activated partial thromboplastin time; ANA: Anti-nuclear antibody; Anti-dsDNA: Anti-double stranded deoxyribonucleic acid; ANCA: Anti-neutrophilic cytoplasmic antibody; Anti-GBM: Anti-glomerular basement membrane; ASO: Anti-streptolysin O; Hb: Hemoglobin; TRP: Tubular reabsorption of phosphate; Ca/Cre: Calcium/creatinine.

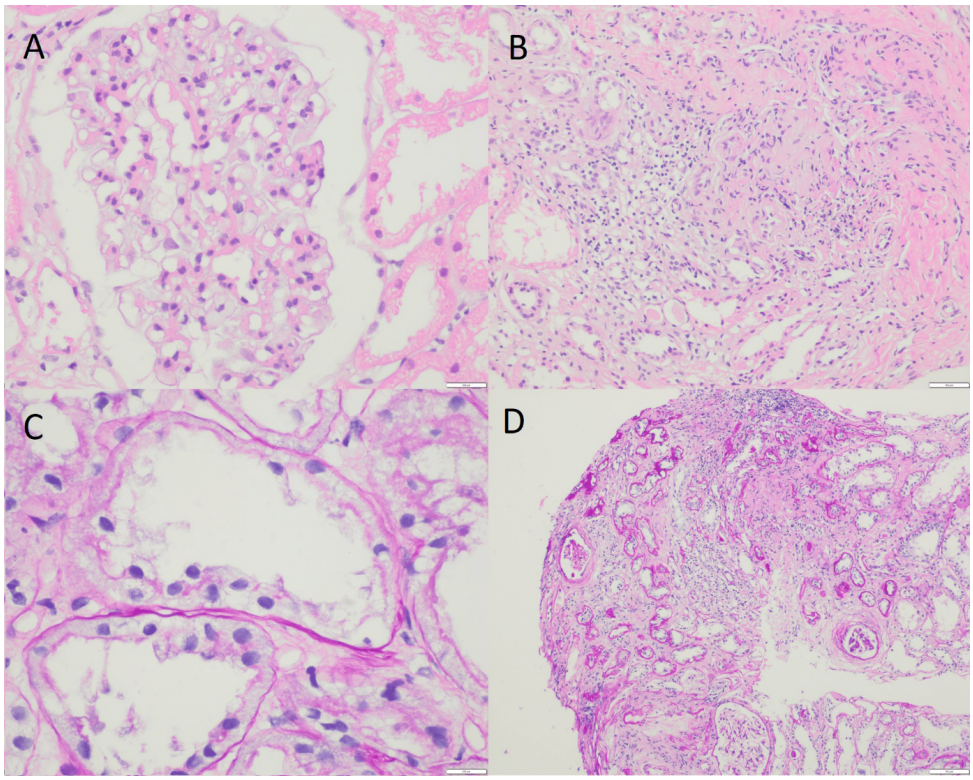

Figure 1. Light microscopy images of kidney biopsy performed on admission.

A) Mild mesangial matrix increase, B) An edematous appearance in the interstitium with mononuclear inflammatory infiltrates, C) Diffuse acute tubular injury characterized by cytoplasmic vacuoles, flattening of the epithelium, and nuclear loss, D) Periglomerular fibrosis and ischemic collapse

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Discussion

Alport syndrome is an inherited kidney disease characterized by hematuria, proteinuria, HT, progressive kidney failure, hearing loss, and ocular pathologies [1]. Eighty-five percent of cases of Alport syndrome are X-linked and caused by a mutation in the *COL4A5* gene, and the remaining 15% have autosomal recessive/dominant inheritance caused by mutations in *COL4A3* or *COL4A4* genes [3]. A lamellar or uniformly thinned glomerular basement membrane (GBM) makes the Alport syndrome have a pathognomonic histologic appearance, which can be demonstrated via electron microscopy [4]. Light microscopy shows nonspecific findings, including mesangial matrix expansion and hypercellularity, but when the disease progresses, the only histologic finding can be secondary focal segmental glomerulosclerosis (FSGS) and interstitial fibrosis. The reason for FSGS development is heterogeneous, but changes in the filtration barrier are the main factors in the pathogenesis [3, 5].

Type IV collagen consists of alpha (a) chains, including a3, a4, and a5, and these chains ensure that type IV collagen forms helical heterotrimers in the endoplasmic reticulum in podocytes. If there is a mutation in the *COL4A5* gene, this helical heterotrimer structure cannot be formed and type IV collagen cannot be secreted into the GBM. The accumulation of misfolded proteins inside the podocyte causes the activation of the unfolded protein response pathway, leading to cytotoxicity and apoptosis. Besides, it can cause podocyte detachment leading to FSGS in the long term [3]. The development of glomerulosclerosis also may lead to impairment in the glomerular perfusion due to vascular occlusions [6]. The ischemic collapse in the glomeruli may occur secondary to the hypoperfusion process, as in our patient.

In our patient, a hemizygous mutation in the *COL4A5* gene confirmed X-linked Alport syndrome diagnosis and FSGS was observed histopathologically using light microscopy in the kidney biopsy. There is no specific treatment to correct the underlying defect for Alport syndrome. In patients with overt proteinuria and HT, angiotensin blockade can be administered for antiproteinuric and antihypertensive effects and it aids in slowing the progression of the disease [1]. Therefore, our patient was treated with an ACEi and the proteinuria level regressed to less than 1 g per day. Supportive measures are used for hearing loss and ocular impairment in affected patients. Kidney replacement therapies with dialysis or kidney transplantation can be applied in patients with Alport syndrome who develop kidney failure and the latter modality is most preferred. Recurrent disease is not expected to occur in the transplant, since the donor type IV collagen and GBM are normal [1].

Renal tubules are one of the main components of the kidney and the major sites in response to injuries. They are vulnerable to various conditions, such as hypoxia, proteinuria, nephrotoxic substances, including heavy metals, metabolic diseases, or aging [7]. In response to injury, tubular epithelial cells undergo changes and function as inflammatory and fibrogenic cells that cause interstitial inflammation and fibrosis. Thus, these damaged renal tubule cells can lead to the progression of kidney disease [8]. Kidney impairment may also manifest as acute tubular necrosis (ATN) in Pb and Hg exposure [2]. In our patient, body Pb and Hg levels were high. Besides, the kidney biopsy clearly showed diffuse acute tubular injury. Therefore, we believe that in addition to the presence of previously undiagnosed Alport syndrome, the patient also had nephrotoxic kidney injury due to exposure to these metals.

Pb is an element found in gasoline and batteries and used as a pigment in paints. In case of toxicity, the nervous, circulatory, skeletal, renal, hematopoietic, or endocrine systems are affected. Affected individuals may experience headaches, seizures, ataxia, learning difficulties, and hyperactivity [9]. The kidney is one of the organs where Pb is primarily accumulated. The action of Pb in kidney cells occurs in several different ways. It can cause kidney damage by decreasing mRNA expression of enzymes that inhibit oxidative stress and increasing mRNA expression of transforming growth factor-β1 (TGF-β1), monocyte chemoattractant protein-1 (MCP-1), and alpha-2 macroglobulin (α-2M), which increase inflammation [10].

Many previous studies have reported a positive correlation between Pb exposure and HT [11-13]. The exact mechanisms underlying the HT due to Pb exposure are unknown, but it can be attributed to Pb nephropathy [13]. Pb exposure causes oxidative stress and reduces nitric oxide availability. Therefore, the exposure increases systemic vascular resistance and causes HT [14]. Our patient had HT on admission and during the follow-up, but despite a history of exposure to Pb, he also had genetically proven Alport syndrome, which may cause HT. Therefore, it would not be appropriate to attribute the presence of HT to an isolated etiology in our case.

As stated previously, Pb intoxication can cause ATN. It also may lead to Fanconi syndrome development by inducing generalized defects in solute and amino acid transport in acute exposure, and progressive tubulointer-

stitial nephritis with leukocyte infiltration, interstitial fibrosis, and tubular atrophy in chronic exposure [15]. Our patient had proteinuria, glucosuria, and phosphaturia suggestive of Fanconi syndrome on the first admission. Besides, the kidney biopsy showed signs of inflamed interstitium and acute tubular damage, as well as tubular atrophy and fibrosis. As a result, we consider that kidney tubulointerstitial damage developed due to Pb intoxication in the patient who still had high urinary Pb levels a certain time after discontinuation of exposure. The risk of renal damage increases parallel to the rise in the Pb levels and GFR decreases accordingly [15, 16].

In the treatment of Pb intoxication, a 20% increase in GFR can be achieved with Ca-EDTA chelation. With the combination of thiamine and ascorbic acid, Pb is mobilized from the tissues and excreted in the urine, and biochemical abnormalities are corrected [10]. Chelation was not started in our patient, but improvement was observed with thiamine and ascorbic acid in the laboratory findings that were suggestive of Fanconi syndrome, and the urinary Pb levels were normalized in the follow-up.

Hg exposure is related to occupational, environmental, and dietary factors. It is rapidly absorbed from the gastrointestinal tract and reaches the target organ by entering the blood circulation. However, the most common human exposure to Hg occurs through the inhalation of Hg vapor via occupational exposure, as in our patient [17]. The primary site of accumulation is the kidneys, especially the proximal tubules. The Hg taken into the cell binds to thiol-containing protein/non-protein molecules with a strong bond and is prevented from leaving the cell [14]. Hg-associated kidney damage can be due to tubular dysfunction with elevated urinary excretion of albumin, transferrin, retinol-binding protein, and β-galactosidase. On the other hand, in low-dose chronic exposure, the accumulation of complement (C3) and immunoglobulin (IgM and IgG) in the GBM, membranous glomerulonephritis, and tubulointerstitial damage can be seen in kidney biopsy [8, 10, 18]. Additionally, by a similar mechanism to Pb, exposure to Hg causes oxidative stress, impaired nitric oxide signaling, modified vascular response to neurotransmitters, and disturbed vascular muscle Ca^{2+} signaling, leading to HT [18].

Acute Hg exposure produces acute dyspnea, abdominal pain, altered mental status, increased salivation, vomiting, and tremor, whereas chronic exposure causes skin lesions and neurological disturbances, such as hearing loss, paresthesia, and ataxia [8, 10, 18]. Although our patient was acutely exposed to Hg by inhalation, he did not have any respiratory distress, but he had complaints of nausea and vomiting. In addition, although HT was detected in our patient, as mentioned before, it was not possible to explain the true mechanism of HT in our patient. Also, although he had massive proteinuria on admission, no staining was detected in the immunofluorescence examination and no pathological finding suggestive of membranous nephropathy was found in kidney biopsy. Finally, as the patient had diffuse tubulointerstitial damage, we attributed these findings as secondary to Hg and/or Pb intoxications.

The treatment of acute Hg intoxication consists of removal of the element from the cell with agents, such as 2,3-dimercaptopropane-1-sulfonic acid (DMPS) and 2,3-dimercaptosuccinic acid (DMSA), which chelate metals [1]. Interestingly, NAC also appears to mediate the extraction of mercuric ions following exposure of rats [10]. Additionally, a previous study showed that although dietary selenium and vitamins C and E did not reduce Hg bioaccumulation, they increased overall survival with anti-oxidant effect by reducing serum lipid peroxidation [19]. Considering the lack of Hg exposure for the last two months, chelation treatment was not commenced in our patient. However, as blood and urine Hg levels were still mildly elevated, a combined treatment containing NAC and vitamins C and E was started, and urine and blood Hg levels returned to normal during the follow-up.

Conclusion

A patient with asymptomatic genetic kidney disease with the potential of progressing to kidney failure may have accelerated worsening of kidney functions due to occupational exposure to heavy metals. Regarding the initial diagnosis with current clinical and laboratory findings in patients, it is noteworthy that there is always the possibility of another pathology, and additional investigations may be needed. Also, in examining public health issues and the financial burden caused by occupational diseases, the importance and necessity of creating safer work environments and frequent inspections should be considered.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research. Written informed consent was obtained from the patient and his parents for the use of the patient's clinical and laboratory data for scientific purposes in a confidential manner.

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Authors' contributions

Conceptualization: Emre LeventoÄŸlu, Bahriye Uzun Kenan and Bahar Büyükkaragöz; Visualization: Bahar Büyükkaragöz and Kibriya Fidan; Investigation: Betül Öğütand and İpek Işık Gönül; Data curation: Emre LeventoÄŸlu and Bahar Büyükkaragöz; Writing the original draft: Emre LeventoÄŸlu, Bahriye Uzun Kenan: and Bahar Büyükkaragöz; Review, and editing: Bahar Büyükkaragöz. and Kibriya Fidan; Supervision: Bahriye Uzun Kenan and Kibriya Fidan.

Conflict of interest

The authors declared no conflict of interests.

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