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Renal involvement in a silicosis patient – case report and literature review

Fei-Fei Chen[a,b,c*], Hai-Yan Tang[d*], Feng Yu[a,b,c,e], Cheng-Li Que[d], Fu-de Zhou[a,b,c], Su-Xia Wang[a,b,c], Guang-Fa Wang[d] and Ming-Hui Zhao[a,b,c]

[a]Renal Division, Department of Medicine, Peking University First Hospital, Beijing, P.R. China; [b]Institute of Nephrology, Peking University, Beijing, P.R. China; [c]Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, P.R. China; [d]Department of Respiratory and Critical Care Medicine, Peking University First Hospital, Beijing, P.R. China; [e]Renal Division, Peking University International Hospital, Beijing, P.R. China

ABSTRACT

A 43-year-old Chinese man with a silicosis history was admitted to our hospital due to bilateral lower extremity edema for 1 year, exacerbating with hematuria for 2 months. He started working as a coal miner 30 years ago, and was diagnosed as silicosis 3 months ago. Lab tests revealed hematuria 3+, proteinuria 3+, and a serum creatinine value 2.47 mg/dl on routine check. He was diagnosed with focal proliferative IgA nephropathy (IgAN) and acute tubulo-interstitial nephritis by renal biopsy. He was treated with corticosteroids and got a remission 4 months later. Immunohistochemical staining showed the deposition of macrophage receptor with collagenous structure (MARCO), nod-like receptor pyrin domain-containing-3 (NLRP3), Caspase-1, apoptosis-associated speck (ASC), interleukin (IL)-1β, and IL-18 in both glomerular and tubulo-interstitial areas. We proposed that the silicon exposure could be related to his kidney disease in the patient and NLRP3 mediated inflammation might be involved in its pathogenesis which needs further explorations.

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Silicosis; silica nephropathy; IgA nephropathy; MARCO receptor; the NLRP3 inflammasome

Introduction

Silicosis is the most common one in pneumoconiosis, which was defined as a fibrotic lung disease caused by inhalation of free crystalline silicon dioxide or silica. Occupational exposure to repairable crystalline silica dust particles occurred in many industries, like sand-blasters, miners, quarry workers, *etc*. [1] It was reported that silica exposure was associated with several disorders, including autoimmune diseases [2,3], renal diseases[4,5], *etc*.

Although the alveolar macrophages are believed to initiate the inflammatory responses of silicosis, its true mechanism remained to be elucidated. It was proposed that mechanical stimulation, chemical poisoning, oxygen radical, and immune reaction might be involved in the pathophysiological development of the disease [6,7].

More interestingly, recent studies suggested that nod-like receptor pyrin domain-containing-3 (NLRP3, also called cryopyrin or NALP3) inflammasome (a cytoplasmic multi-protein which was consisted of a sensor NLRP3, an apoptosis-associated speck (ASC) adaptor, and an effector caspase-1 and regulated the mutation and secretion of pro-inflammatory cytokines like interleukin (IL)-1β and IL-18 played a vital role in the inflammatory response and subsequent development of pulmonary fibrosis in silicosis [8–12]. NLRP3 inflammasome was also related to several crystal-associated renal diseases, like gout, oxalate nephropathy, *etc*. [11,13].

Herein, we described a patient with renal biopsied proven injury who had a history of silicosis, and the NLRP3 pathway related to the association of silicosis and the kidney disease was further explored.

Case presentation

Clinical history and laboratory data

A 43-year-old Chinese Han man was admitted to our hospital because of edema of lower limbs bilaterally for 1 year, exacerbating with gross hematuria in the last 2 months.

CONTACT Feng Yu yufengevert1@sina.com Renal Division, Department of Medicine, Peking University First Hospital, Beijing, P.R. China; Cheng-li Que quechengli@hotmail.com Department of Respiratory and Critical Care Medicine, Peking University First Hospital, Beijing, P.R. China
*These authors contributed equally to this article.

One year ago, he developed pitting edema of lower limbs and also found bubbles in urine at the same time. He visited the local hospital and the diagnosis of lower limbs varicose vein was made. Ten months later, his edema aggravated consciously and he presented with the whole course gross hematuria. The routine urinalysis showed proteinuria (3+) and hematuria (3+). Urinary protein excretion amount was 3.7 g/24h. The serum creatinine value was in the normal range and increased to 2.47 mg/dL one month later.

The past history revealed that he was a coal miner for 30 years and diagnosed as silicosis 3 months ago. He presented with hypertension for 4 years and it could be controlled at the range of 120–130/80–90 mmHg by regular medications. He did not abuse alcohol, cigarettes, or other drugs.

After admission, physical examination revealed that his temperature was 36.5 °C, respiratory rate was 20 breaths/min, pulse rate was 76 beats/min and blood pressure was 130/80 mmHg. There was no jaundice, rash and bleeding by skin examination and the superficial lymph nodes was not touched. Pitting edema of lower limbs was found bilaterally.

Table 1 summarized all the laboratory indices after his admission.

High-resolution computed tomography (HRCT) showed that there were multiple small nodular lesions on both lung fields and multiple calcifications were on the left upper lobe.

Ultrasound showed that the left and right kidneys were both in normal size. No stenosis or thrombus of renal artery and vein were found by Doppler ultrasound.

The patients presented with nephritic syndrome and acute kidney injury (AKI), which could not be excluded with silicosis associated renal disease. Thus, renal biopsy was crucial for the diagnosis and it was performed after his admission.

Diagnosis

His renal biopsy specimen was examined by light microscopy, immunofluorescence, and electron microscopy. By light microscopy, 23 glomeruli were included in the specimen. One glomerulus was ischemic sclerosed and the remaining glomeruli manifested as mild mesangial cell and matrix proliferation with segmental endocapillary hypercellularity. Fuchsinophilic deposits were observed in mesangium. There were one cellular crescent and four fibro-cellular crescents. Tubular epithelial cells showed cytoplasmic vacuolization and focal loss of brush border with focal tubular atrophy. There was moderately interstitial infiltration of lymphocytes, mononuclear cells and a few eosinophils with focal interstitial fibrosis. Arterioles were thickened with hyalinosis. Immunofluorescence revealed lump and granular staining of IgA (3+) and C3 (3+) in mesangium and others including IgG, IgM, C1q, and fibrin were all negative (Figure 1(a–f)).

By electron microscopy, mild mesangial expansion with electron dense deposits in mesangial and paramesangial matrix were observed. No remarkable changes were seen in glomerular basement membrane and the foot processes of podocytes were effaced diffusely (Figure 2(a,b)).

The final pathological diagnosis was focal proliferative IgA nephropathy (Oxford classification: M1E1S0T1) and acute tubulo-interstitial nephritis.

Based on the renal pathological findings and his occupation, we proposed that the kidney disease might

Table 1. Laboratory indices of the patient.

Urinalysis		Blood chemistry		Serology	
Protein	2+	Sodium	141.80 mmol/L	C-reactive protein	2.05 mg/L
Glucose	–	Potassium	3.52 mmol/l	Rheumatoid factor	<20 IU/ml
Sediments		Chloride	105.70 mmol/L	Antistrptolysin	33.10 IU/ml
Red blood cell	170–180/high-power field	Blood urea nitrogen	13.30 mmol/L	Antinuclear antibodies	1:100
Hyaline cast	0	Creatinine	2.51 mg/dl	Anti-ENA autoantibodies	–
Granular cast	0–1/high-power field	Total protein	63.10 g/L	MPO-ANCA	–
RBC cast	0	Albumin	35.90 g/L	Anti-GBM	–
		Total bilirubin	13.00 μmol/L	PR3-ANCA	–
		Aspartate aminotransferase (AST)	17 IU/L	Immune globulin G (IgG)	9.99 g/L
Pulmonary function test		Alanine transaminase (ALT)	22 IU/L	IgA	3.19 g/L
Vital capacity (VC)	3.93 L	**Peripheral blood**		IgM	0.80 g/L
VC%pred	83.6%	Peripheral blood	112 g/L	Complement 3	1.09 g/L
Forced expiratory volume in 1.0 s (FEV1.0)	3.12 L	Platelet	248×10^{12}/L	Complement 4	0.22 g/L
FEV1.0%	84.4%	White blood cell	9.20×10^{9}/L	Anti-hepatitis B and C virus antibody	–
DLCO%pred	69.7%	Erythrocyte sedimentation rate	40 mm/h	Immunofixation electrophoresis	No monoclonal lane

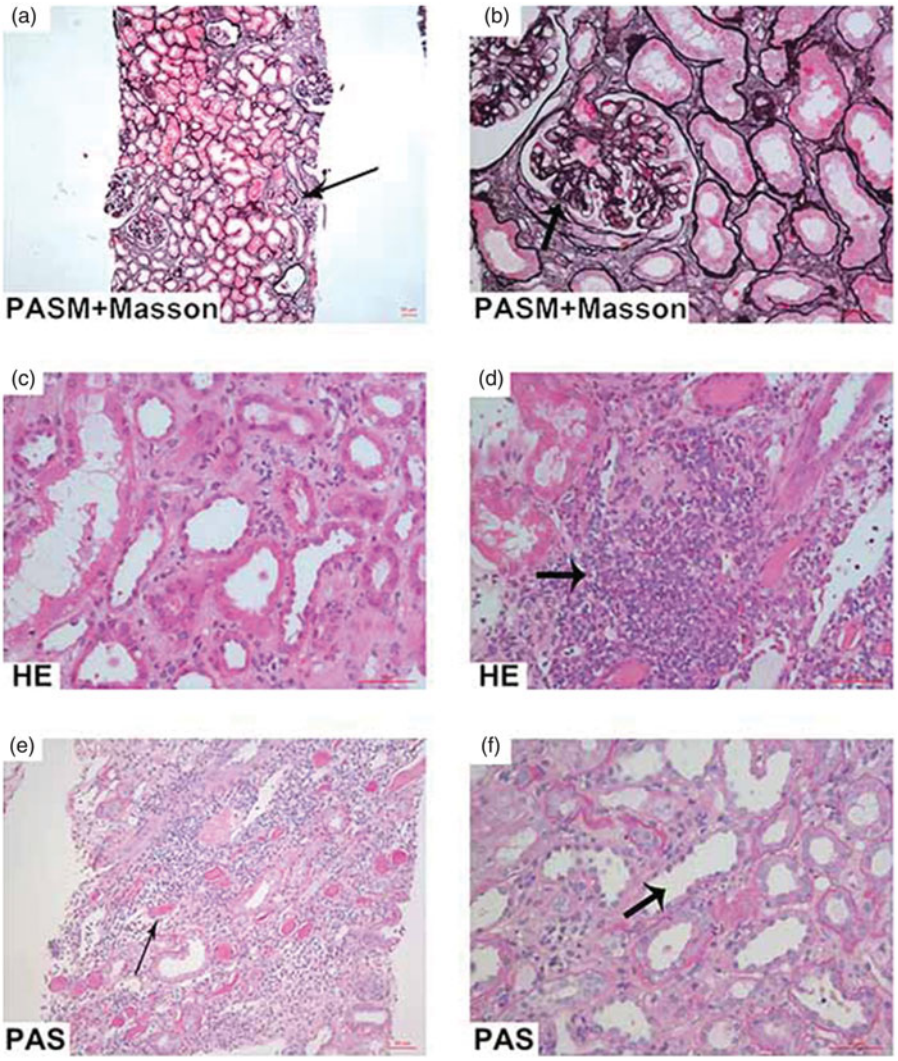

Figure 1. The renal pathological findings. (a, b) PASM-Masson stain, (left ×100, right ×400) showed focal interstitial fibrosis accompanied by collections of interstitial inflammatory cells (left arrow). The renal capsules adhered (right arrow) with atrophic tubules and focal tubule dropout. (c, d) Hematoxylin-Eosin stain, (×400) showed inflammatory cell infiltrate (arrow), including lymphocytosis, mononuclear cells and a few eosinophils. (e, f) Periodic acid-Schiff stain, (left ×200, right ×400) showed a massive protein casts in the dilated tubules (left arrow) accompanied by brush border of proximal tubule dropout (right arrow).

be associated with the silica exposure. Then, the kidney sections of the patients were further scanned using polarization microscopy for the quantity of silica or silicon dioxide crystal deposition. However, we did not find silica or silicon dioxide crystal deposition neither in glomerulus nor tubulo-interstitial areas (Figure 2(c)).

As the NLRP3-mediated inflammation might be involved in the oxalate nephropathy and silicosis, the MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 were further stained by immunohistochemistry which were all positive in both glomerular and tubulo-interstitial areas in our patient and they were all virtually negative in the normal control (normal part of one nephrectomized kidney due to renal carcinoma) (Figure 3(a–x)). Furthermore, we selected one primary IgA nephropathy patient (Oxford classification: M1E1S0T1) as the disease control and we found that the expressions of MARCO, ASC, Caspase-1, and IL-1β were similar with our patient. However, the staining of NLRP3 was significantly higher in tubulo-interstitial areas than that in glomerular areas in the disease control, and the staining of IL-18 was specifically expressed in the distal convoluted tubules and some part of glomerular areas in our patient and it was dispersive around glomerular and tubulo-interstitial areas in the primary IgA nephropathy patient (Figure 4(a–x)).

Follow-up

As the patient was diagnosed as IgA nephropathy combined with acute tubulo-interstitial nephritis, the prednisone (30 mg/d) was then initiated with tapering

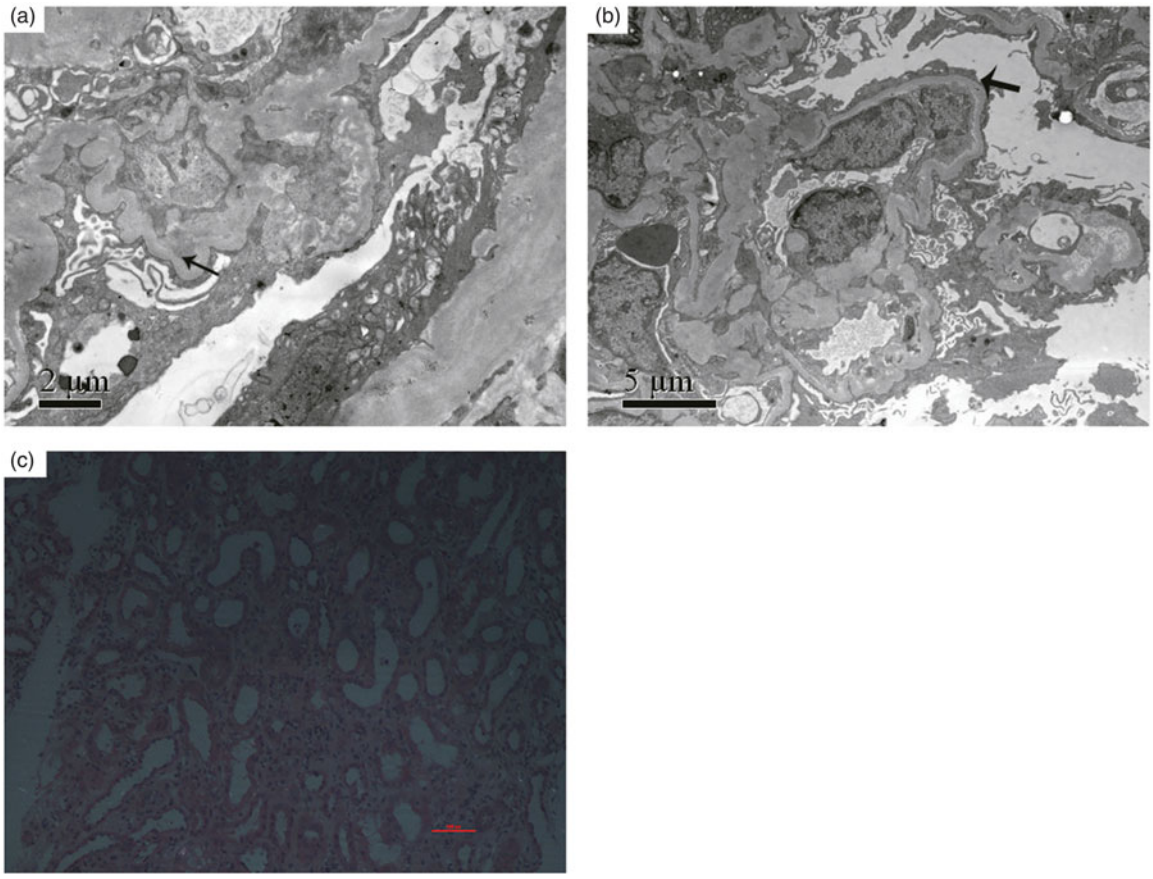

Figure 2. The results of electron microscope and polarization microscope. (a) Electron microscopy showed mesangial electron dense deposits (arrow) with matrix increase. (b) Electron microscopy showed diffuse visceral epithelial cell foot process effacement (arrow). (c) Polarization microscopy showed no silica or silicon dioxide crystal deposition neither in glomerulus nor tubulointerstitial areas.

regularly in combination with ACEI treatment. The patient got a significant improvement both for renal function and proteinuria after 2 months, which kept stable still now. He also changed his job to remove the occupational factor. His laboratory data at follow-up were showed in Table 2.

Discussion

Occupational exposure to silica or silicon dioxide dust has been examined as a possible risk factor with respect to several diseases, like tuberculosis, lung cancer [14], systemic vasculitis [15], rheumatoid arthritis [16], systemic sclerosis [17], systemic lupus erythematosus [18], renal involvement [19], *etc*.

Early in 1951, Saita G et al. [20] firstly reported that the renal functions were decreased in some silicosis patients. Subsequently, several epidemiological evidences suggested that the silica exposure was associated with an increased risk of end-stage renal disease (ESRD), chronic kidney disease (CKD), or specifically glomerulonephritis [21–24]. Our patient had a history of silicosis and was diagnosed with focal proliferative IgA nephropathy and acute tubulo-interstitial nephritis by renal biopsy. We proposed that his renal disease might be associated with the silicosis history.

Silica nephropathy referred to the floorboard of kidney diseases after exposure to silica or silicon dioxide, including tubulo-interstitial disease, immune-mediated disease, chronic kidney disease, and end-stage renal disease [25–29]. In literatures, the renal histopathology of silica nephropathy was varied, including focal glomerulonephritis, necrotizing glomerulonephritis, crescentic glomerulonephritis, *etc*. [25–46] (Details in Table 3).

The mechanisms underlying silica nephropathy have not yet been fully elucidated. Most evidences were consistent with the interplay of at least the following two ways: the direct toxic effect of the deposited crystalline material in the renal parenchyma or an autoimmune process involving interaction of silica particles with the immune system, mainly by activation of macrophages through which the kidneys were affected [22,29,47].

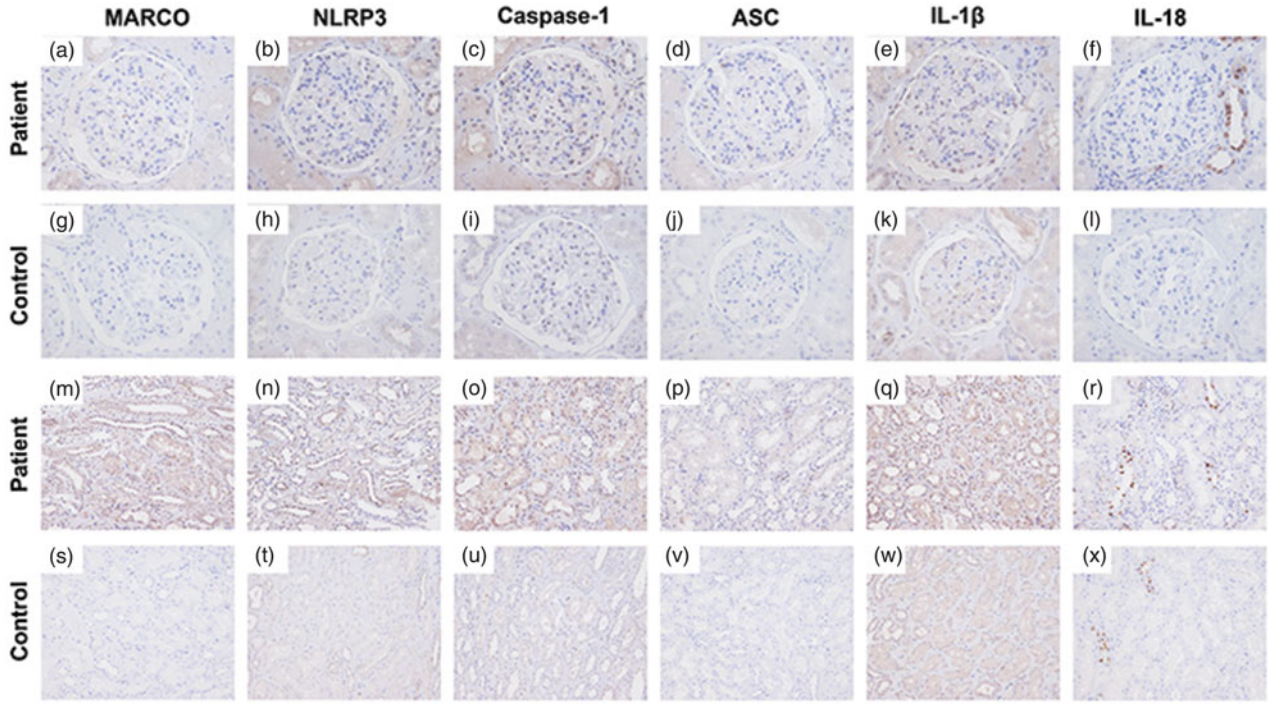

Figure 3. Immunohistochemistry staining for MARCO, NLRP3, Caspase-1, ASC, IL-1β, IL-18 in the patient and the normal control (an adult kidney biopsy obtained from nephrectomy away from cancer). (a–f) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in glomerulus of the patient, respectively, (×400). (g–l) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in glomerulus of the normal control, respectively, (×400). (m–r) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in tubulo-interstitial areas of the patient, respectively, (×200). (s–x) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in tubulo-interstitial areas of the normal control, respectively, (×200).

More importantly, scavenger receptor, especially the macrophage receptor with collagenous structure (MARCO) expressed in alveolar macrophages [48–52] and the associated NLRP3 inflammasome were thought to be the key regulators for binding and uptake of crystalline silica particle, recognition and clearance of silica and the subsequent development of pulmonary fibrosis in recent studies [3,8,9,11]. NLRP3 inflammasome could be activated after uptake of silica by scavenger receptors, lysosomal rupture and release of cathepsin B [53]. Then, it could cleave several proinflammatory cytokines leading to the secretion of IL-1, IL-18, *etc*.

Positive depositions of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in the glomerular and tubulo-interstitial areas of our patients further highlight their roles in the pathogenesis of silica nephropathy. Interestingly, the immunohistochemistry results from the disease control of one primary IgA nephropathy patient showed that the distributions of MARCO, Caspase-1, ASC, and IL-1β were not different between our patient and disease control and the expression of IL-18 was mainly expressed in the distal convoluted tubules and some parts of glomerular areas in our patient although it was dispersive around glomerular and tubulo-interstitial areas in the primary IgA nephropathy patient. More importantly, we found that the staining of NLRP3 was significantly higher in tubulo-interstitial areas than that in glomerular areas in the disease control, which was consistent with the previous work by Chun J in primary IgA nephropathy [54]. They found that in primary IgA nephropathy, NLRP3 principally expressed in tubular areas with lesser glomerular localization. Firstly, they detected NLRP3 localization in normal human renal tissues and biopsies from primary IgA nephropathy patients by immunochemistry and immunofluorescence (IF). The results suggested that NLRP3 predominately localized on tubular epithelium with almost no expression in glomerular areas in normal human kidney by IF. Then, they concentrated on tubular expression of NLRP3 and discovered the high expression of NLRP3 (protein and mRNA) in human primary renal tubular cells (HPTC) through immunostaining and mRNA analyzing. Also, when HPTC lost their epithelial phenotype and obtained the characteristic of fibroblastic phenotype by persistent stimulation of TGF-β1 which led to chronic tubular epithelial cell and fibrosis, NLRP3 expression (protein and mRNA) was decreased obviously. Moreover, NLRP3 mRNA

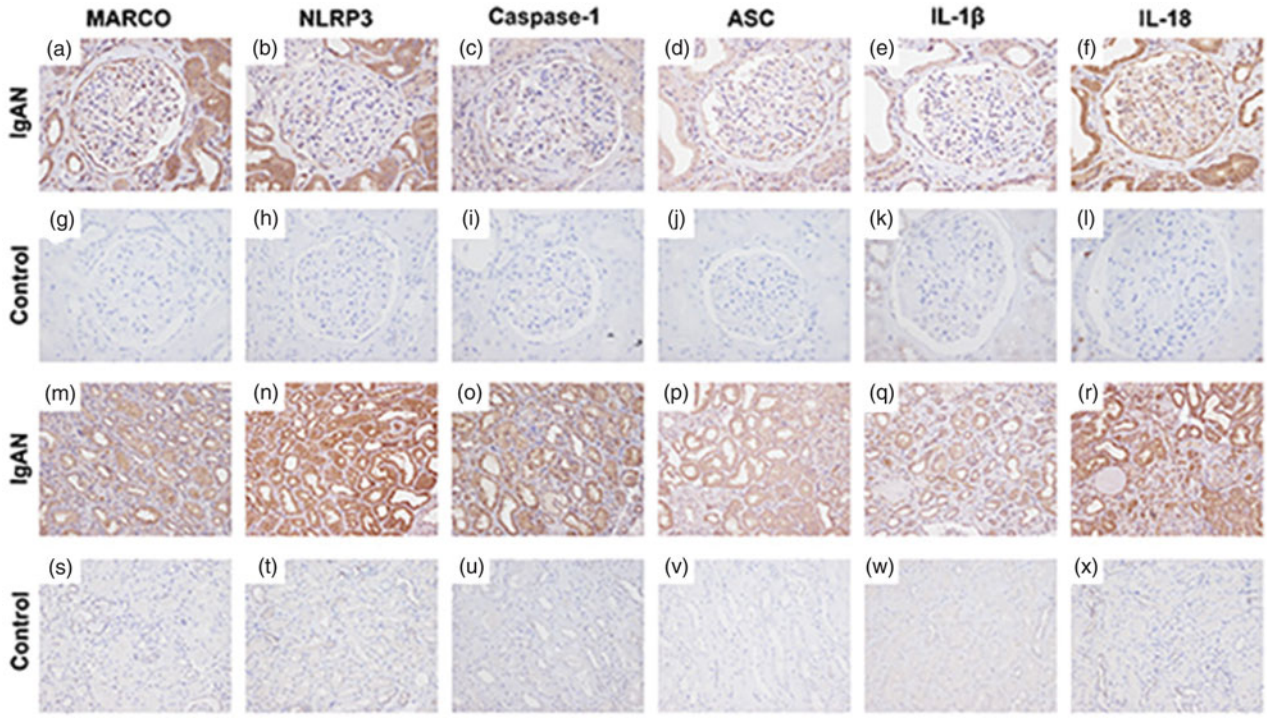

Figure 4. Immunohistochemistry staining for MARCO, NLRP3, Caspase-1, ASC, IL-1β, IL-18 in a primary IgA nephropathy (IgAN) patient and the normal control (an adult kidney biopsy obtained from nephrectomy away from cancer). (a–f) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in glomerulus of the primary IgAN patient, respectively, (×400). (g–l) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in glomerulus of the normal control, respectively, (×400). (m–r) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in tubulo-interstitial areas of the primary IgAN patient, respectively, (×200). (s–x) Immunohistochemical staining of MARCO, NLRP3, Caspase-1, ASC, IL-1β, and IL-18 in tubulo-interstitial areas of the normal control, respectively, (×200).

Table 2. Clinical data of the patient at follow-up.

	Initial	18 February 2014	8 April 2016	28 July 2018	21 September 2018	11 November 2018	27 January 2019	17 March 2019	10 May 2019	22 June 2019
Prednisone	/	30								
Qd	withdrawal	/	/	/	/	/	/	/		
Urine										
Proteinuria	++	++	±	−	−	−	+	+	±	++
Proteinuria amount (g/24h)	3.41	2.84	0.21	/	/	/	/	/	/	0.37
Hematuria	+++	+++	±	−	−	−	+	+	−	−
Blood chemistry										
Creatinine (mg/dl)	2.51	1.79	1.53	1.26	1.27	1.27	1.29	1.07	1.20	1.19
Albumin(g/L)	35.9	37.4	42.5	41.5	42.3	41.6	41.2	43	41.9	42.5

expression of renal biopsies was detected by real-time PCR in fifty-four primary IgA nephropathy patients. They found that NLRP3 mRNA expression levels in renal biopsies from IgA nephropathy patients were two to several hundred-folds higher than normal controls. IgA nephropathy patients with high levels of NLRP3 expression had less risk of the composite endpoint compared with low expression of NLRP3 patients. Furthermore, in progressive IgA nephropathy, NLRP3 expression of renal tissues was decreased during tubular atrophy/interstitial fibrosis (the best predictor of outcome in IgA nephropathy upon established on the Oxford classification) which was connected with a worse clinical outcome. Therefore, they pointed that NLRP3 was a predominant tubular protein in primary IgA nephropathy. A recent study by Mascarenhas S et al. [55] found that silica had nephrotoxicity on human-kidney proximal-tubular cells (the toxin's prime targets) *in vitro*, which exhibited by induction of prolonged tubular-cell apoptosis and inflammation, through NLRP3-mediated pathway. Thus, we proposed that the kidney disease of our patient might be a secondary IgA nephropathy

Table 3. Cases describing silicosis combined with renal pathological changes in literatures.

Year	Author	Case descriptions	Renal pathologic features	References
1975	Saldanha LF et al.	A 44-year-old man with history of significant industrial silica exposure who presented with hypertension and proteinuria.	Focal glomerulonephritis, intraluminal sloughing of the proximal convoluted tubule, cytoplasmic vacuolization and granularity.	[25]
1977	Suratt PM et al.	Four men developed silicosis after sandblasting tombstones for an average of 35 months and two of them developed lupus erythematosus and focal glomerulonephritis respectively.	Mild proliferative glomerulonephritis.	[30]
1978	Giles RD et al.	A 23-year-old sandblaster who developed acute onset massive proteinuria and fatal renal failure.	Mild proliferative glomerulonephritis with loss of colloidal iron staining for sialoprotein, and electron microscopy disclosed an increased density of epithelial cytoplasm, altered lysosomes and endothelial cell microtubular structures.	[26]
1980	Hauglustaine D et al.	A 37-year-old white male, working in a tile factory, presented proteinuria with no obvious tubular dysfunctional.	Mild focal segmental proliferative glomerulonephritis. Distinct alterations were found by electron microscopy, especially in the proximal tubular cells.	[31]
1981	Bolton WK et al.	Rapidly progressive renal failure developed in 4 patients with silica exposure. 3 presented with manifestations of a connective tissue disorders. All had abnormal proteinuria, hypoalbuminemia and active urinary sediments.	Glomerular hypercellularity and sclerosis, crescents, interstitial cellular infiltrates and tubular necrosis with red cell casts as seen on light microscopy. On electron microscopy there was foot process obliteration, characteristic cytoplasmic dense lysosomes, microtubules and dense deposits.	[32]
1983	Cledes J et al.	A 59-year old sand-blaster, histologically proven silicosis was complicated by systemic lupus erythematosus (SLE) and nephritis.	Focal glomerulonephritis with IgG, IgA and C1q deposits.	[33]
1983	Banks DE et al.	A coal miner presented with pulmonary changes consistent with acute silico lipoproteinosis who developed proteinuria and hematuria.	Diffusely thickened glomerular basement membrane, foot process effacement, and dense lamellar inclusions in swollen glomerular epithelial cells, similar to those seen in Fabry's disease.	[34]
1987	Osorio AM et al.	A 54-year-old foundry worker with extensive silica exposure, developed the nephrotic syndrome and renal failure over a 3-month period.	Proliferative glomerulonephritis.	[27]
1987	Bonnin A et al.	Three men, (50, 67 and 69 years old) with the history of pulmonary silicosis, and two of them presented with microscopic hematuria, mild renal failure, and high blood pressure, and all had glomerular type proteinuria.	Crescentic IgA mesangial nephropathy.	[28]
1989	Arnalich F et al.	A 55-year-old white male, with silicosis diagnosed 10 years earlier, presented massive proteinuria with microscopic hematuria, moderate renal failure and distal polyneuropathy.	Focal segmental necrotizing glomerulonephritis and arteriolitis.	[35]
1989	Sherson D et al.	A 56-year-old man worked as a sandblaster for 30 years, and had rapidly progressive crescentic glomerulonephritis.	Severe crescentic glomerulonephritis with significant edema and cellular infiltration in the interstitium.	[36]
1990	Dracon M et al.	A series of 11 coal miners demonstrating a progressive renal failure with a syndrome of rapidly progressive glomerulonephritis and 3 of them had IgA deposition.	Crescentic glomerulonephritis.	[37]
1991	Pouthier D et al.	A 43-year-old stone cutter with 13 years of exposure to silica developed a pulmonary silicosis and a glomerulonephritis with moderate renal failure.	Segmental and focal mesangial proliferation and on electron microscopy, distinct alterations of the proximal tubular cells.	[38]
1994	Neyer U et al.	A 55-year-old male had Wegener's granulomatosis after silica exposure.	Severe active glomerulonephritis with intra- and extra-capillary proliferation and crescents in more than 50% of the glomerulus.	[39]
1996	Wilke RA et al.	A 58-year-old coal miner as an employee of the chemical industry suffered from end-stage renal disease.	Glomerulosclerosis and chronic interstitial nephritis	[40]
2001	Nakajima H et al.	A 63-year-old man had the history of silicosisand had been diagnosed as glomerulonephritis.	Pauci-immune necrotizing crescentic glomerulonephritis	[41]
2001	Fujii Y et al.	A 51-year-old male who had been working as a building wrecker for 20 years suffered from IgA nephropathy.	Mild mesangial matrix expansion and mesangial cell proliferation with IgA deposition.	[42]
2003	Mulloy KB et al.	A 63-year-old male who worked in Department of Energy facilities and was diagnosed as microscopic polyangiitis, systemic necrotizing vasculitis, vasculitis, and glomerulonephritis.	Proliferative (crescentic) and necrotizing glomerulonephritis.	[43]
2010	Dahlgren J et al.	A 38-year-old male was diagnosed as Goodpasture's syndrome after high level of exposure to crystalline silica	Global glomerulonephritis	[44]
2016	Riccò M et al.	A 68-year-old male (smoker) was diagnosed as IgA nephropathy after exposure to magnanimous silica dusts.	Glomerular sclerosis with IgA deposition, signs of diffuse vasculitis and tubular atrophy	[45]
2016	Lee JW et al.	A 56-year-old male presented with silicosis and had an occupational history of precious metal processing for 30 years and a 30 pack-year smoking history, and diagnostic analysis revealed perinuclear ANCA-associated microscopic polyangiitis	Chronic sclerosing glomerulonephritis suggesting ANCA-associated crescentic glomerulonephritis	[46]

which could be associated with silicosis based on the different expressions of NLRP3 and its related cytokines/chemokines. This highlight the further explorations of NLRP3 inflammasome on the patho-mechanism of silica nephropathy.

Conclusion

Silicon exposure might be related to the kidney disease in our patient and the NLRP3 mediated inflammation might be involved in its pathogenesis which needs further explorations.

Disclosure statement

No potential conflict of interest was reported by the authors.

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