CASE REPORT

REVISED Case Report: Silicosis and IgA nephropathy, an exceptional association [version 2; peer review: 1 approved, 1 not approved]

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Abstract

A 57-year-old male who had been working in masonry for 33 years was hospitalized for renal function decline associated with exertional dyspnea. He presented with hypertension and limb edema. Urinalysis revealed an active urine sediment with glomerular proteinuria at 1.5 g/24h and the renal biopsy identified mesangial IgA Nephropathy. Chest tomography scans showed signs of silicosis. The patient received Angiotensin-Converting Enzyme Inhibitors with stable renal function. To our knowledge, the association of silicosis-IgA nephropathy has rarely been reported in the literature. This case highlights the effect of chronic exposure to silica dust and its association with both silica and renal disease.

Keywords

IgA nephropathy; silica nephropathy, silicosis, work environment

Open Peer Review

Approval Status

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11 Nov 2021		

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Mami I:** Conceptualization, Writing – Original Draft Preparation; **Hsinet J:** Writing – Review & Editing; **Tlili S:** Writing – Original Draft Preparation; **Jebali H:** Supervision; **Ben Othmani I:** Data Curation; **Ismail S:** Supervision; **Khouja N:** Validation; **Madiha K:** Data Curation; **Rais L:** Supervision; **Benzarti A:** Validation; **Abdelmajid BJ:** Validation; **Ben Fatma L:** Writing – Review & Editing; **Zouaghi K:** Validation

Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

In this new version:

1. Grammatical errors were corrected.
2. The term "Renal" is replaced with the term "Kidney".
3. NFS was translated to English in the new version and is replaced by complete blood count.

Any further responses from the reviewers can be found at the end of the article

Introduction

Occupational exposure to crystalline silica dust particles may lead to silicosis, which is the most common pneumoconiosis. Silica crystalline is known to be a trigger of autoimmune and chronic kidney diseases.¹ The most common silica nephropathies described to be related to silicosis are crescentic glomerulonephritis, proliferative glomerulonephritis and chronic interstitial nephritis.¹ IgA nephropathy (IgA N) is known to be the most frequent glomerulonephritis. However, silicosis-IgA N is a rare association and very few cases have been reported in the literature.²⁻⁶ The underlying pathophysiology remains to be elucidated.

Hereby, we report the case of a mason with a coexistent silicosis and IgA nephropathy in order to better understand such association.

Case presentation

A 57-year-old Caucasian man was admitted to our department of nephrology for unexplained kidney failure (serum creatinine 207 $\mu\text{mol/l}$, eGFR 26 ml/min) that was discovered during routine exams to follow-up his pernicious anemia, including complete blood count and creatinine. The pernicious anemia was diagnosed two years ago and treated by intramuscular injections of vitamin B12.

The patient had a seven pack-year tobacco smoking history that he stopped 5 years ago.

The professional anamneses revealed that the patient worked as a mason for 33 years in several constructions and public work companies. He was responsible for supervising concreting, masonry, foundations, walls and floors covering as well as painting and finishing. During his professional career, he has been exposed to crystalline silica without wearing respiratory protective equipment.

At admission, physical examination revealed a blood pressure of 150/90 mmHg and edema in lower limbs. Urinalysis showed an active urinary sediment with significant proteinuria (2+) and microscopic hematuria (3+). We also noticed bilateral clubbing. The patient was also eupneic. Chest auscultation showed diffuse bilateral crackles.

Biological investigations revealed a kidney failure with a creatinine level at 207 $\mu\text{mol/l}$, and positive proteinuria at 1.5 g/24 hours (normal range <0.5 g/24 hours), as well as a macrocytic anemia with a hemoglobin level at 11 g/dl (anemia shown by level <13 g/dl) and an elevated C reactive protein level at 67 mg/l (normal range <5 mg/l).

P anti-neutrophil cytoplasmic (p ANCA), c anti-neutrophil cytoplasmic (c ANCA) antibodies and antinuclear antibodies (AAN) were negative. Serum complement level was normal. CT guided percutaneous kidney biopsy as performed using automatic spring loaded needle of 16 gauge under local anesthesia. Thirteen glomeruli were included in the specimen. Five of them were ischemic and sclerotic. The rest of the glomeruli showed focal and segmental mesangial hypercellularity without crescents. There were flocculo-capsular synechiae associated with severe tubular atrophy and interstitial fibrosis. Immunofluorescence revealed granular staining of IgA and C3 in the mesangium. The final pathological diagnosis was IgA nephropathy (Figure 1).

Chest tomography was performed and it revealed fibrosing diffuse interstitial lung disease consisting of bilateral septal thickening, ground-glass opacities and a honeycomb pattern. These aspects predominated at the two bases and on the periphery (Figure 2).

Because of occupational history of prolonged crystalline silica exposure, characteristic radiologic findings and clinical signs, the diagnosis of silicosis was given.

Figure 1. Renal biopsy specimen diagnosed with Ig A nephropathy. A,B: Light microscopic, hematoxylin and eosin- stained ($\times 200$), segmental mesangial hypercellularity. C: Light microscopic, Periodic Acid Schiff ($\times 200$), flocculo-capsular synechiae. D: Immunofluorescence microscopy ($\times 200$), Mesangial IgA deposits.

The patient was put on Angiotensin-Converting Enzyme Inhibitors (Ramipril 5 mg/day) because of its antihypertensive and protein-lowering effects and was referred to the pneumology department to complete the respiratory functional exploration and to treat the silicosis. Kidney function was stable after three months of follow-up.

From a medico-legal point of view, silicosis is considered as a compensable occupational disease, according to the Tunisian list table of occupational diseases.⁷

Discussion

Occupational silica exposure causes not only lung damages, but also involves many other organs.⁸ In fact, it was recently noticed that silica exposure is more frequently associated to autoimmune diseases and systemic manifestations such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis or ANCA-associated vasculitis than the general population.⁸ Little is known about mechanisms, but it has been reported that silica dust triggers autoimmune phenomena.²

Moreover, several authors have reported the association of silicosis with kidney lesions as an occupational disease.⁹ According to Ghahramani, exposure to silica dust can be associated with tubulointerstitial or glomerulonephritis involvement, which often leads to an important risk of end-stage kidney disease.¹ The most common silica nephropathy described in the literature were crescentic glomerulonephritis, proliferative glomerulonephritis and chronic interstitial nephritis.³ IgA nephropathy has been rarely reported even though it is the most common type of glomerulonephritis worldwide.¹⁰ Only a few similar cases were described in the literature.²⁻⁶ A summary of all cases reported has been presented in Table 1.

The underlying mechanism connecting the two entities is probably that silica behaves as an adjuvant to enhance immunologic and inflammatory processes.¹¹ According to the medical history of the association of lung and kidney disease, Endo *et al* had reported that not only the upper tract, but also the lung or lower respiratory tract is a mucosal site

Figure 2. Centrilobular and paraseptal emphysema of the upper lobes, Bronchiectasis, interlobular septal thickening, peripheral bilateral ground-glass opacities, and honeycomb pattern.

protected by IgA.¹² Thus, persistent lung inflammation may stimulate IgA mediated immune mechanisms or activate antibody (IgA) dependent monocytes, which leads to IgA mediated immune abnormalities and mesangial deposition of IgA.¹² This process mimics the immunopathologic features of IgA nephropathy and may confirm that this glomerulonephritis may occur secondary to silicosis. Beshir *et al* revealed serum IgA mean level was significantly higher in the silicosis group compared to the non-silicosis group (315.1 ± 165.3 vs. 154.7 ± 105.1 mg/dl, respectively).¹³

Table 1. IgA nephropathy associated with silicosis: summary of literature.

Author, Year	Age (Y)/ sex	Profession	ABP (mmHg)	Hu	Pr (g/24h)	Serum creatinine	Renal biopsy findings	Treatment
Bonnin A et al. 1987 ²	69/M	Miner	200/100	Yes	3	106 µmol/l	IgA mesangial nephropathy associated to crescents	None
	50/M	Ceramic enamelling	150/90	Yes	1.1	165 µmol/l		PE
	67/M	Miner	190/100	Yes	3	212 µmol/l		None
A R Khan et al 1999 ⁴	45/M	Tunnel construction worker	160/100	Yes	4.2	1.2 mg/dl	IgA nephropathy with deposited interstitial nephritis	-
Fujii Y et al. 2001 ⁵	51/M	Building wrecker	-	Yes	0.294	-	Mesangial proliferation with IgA deposition	
Ricco M et al. 2016 ⁶	68/M	Sandstone cave miner		Yes	2.8	2 mg/dl	Glomerular sclerosis with IgA deposition and tubular atrophy	Immune suppressing therapy
Chen F-F et al. 2019 ³	43/M	Coal miner	130/80	Yes	3.7	2.51 mg/dl	Focal proliferative IgA nephropathy and acute tubulointerstitial nephritis	Corticosteroids + ACEI
Our case	57/M	Mason	150/90	Yes	1.5	207 µmol/l	Mesangial proliferation with IgA deposition associated to tubular atrophy and interstitial fibrosis	ACEI

M: Male; Y: Year; ABP: Arterial Blood Pressure; Pr: Proteinuria; Hu: Hematuria; PE: Plasma exchange; ACEI: Angiotensin-Converting Enzyme Inhibitors.

More interestingly, a recent study may explain the putative link between silicosis and IgA N, which is a NOD-like receptor, pyrin domain-containing 3 (NLRP3). In fact, NLRP3 are the key in the inflammatory process caused by silica: they are involved, in association with alveolar macrophages, in binding and eliminating crystalline silica particles, and thus leading to pulmonary fibrosis in recent studies.^{3,14}

The real mechanism and pathophysiology are still not fully elucidated and need more study to further understand how silica leads to autoimmunity and glomerulonephritis. In our case, simultaneous kidney and pulmonary disease could suggest the hypothesis that Ig A nephropathy might be associated with silica exposure.

In addition, data about silicosis-IgA N treatment is poor and inconclusive, because there are no clinical trials or controlled studies, but only sporadic cases have been reported. According to Ghahramani, there is no specific treatment.¹ However, vasculitis and immune-mediated disease required steroids and cytotoxic agents in addition to reducing exposure to silica crystalline dust.⁸

In our case, steroids or immunosuppressant agents were not required because of the absence of active lesions on kidney biopsy. Thus, only antihypertensive treatment with a nephroprotective effect was initiated in association with a withdrawal from occupational exposure. Moreover, chronic lesions, such as tubular atrophy and interstitial fibrosis might explain the degree of kidney insufficiency and the uselessness of immunosuppressive agents.

Moreover, there is no evident data regarding the course of the association of silicosis and IgA nephropathy. Some authors reported that occupational exposure to silica is associated with an elevated risk of end stage renal disease and thus with high mortality,¹ while others had reported that kidney disease or progression is associated with a worsening lung involvement.¹¹

Conclusion

Silicosis-IgA N is a very rarely reported association in the literature. It seems to be far more than an incidental association. The pathogenesis is still not fully understood, and the paucity of information makes a significant barrier to confirm such a link. Nevertheless, according to many authors, the main underlying mechanism is a triggering of autoimmunity with a mal-adaptive immune response. In addition, it is necessary to be particularly vigilant with these rare associations and to think systematically about environmental and occupational exposure.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of his clinical details and clinical images was obtained from the patient.

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Gisella Vischini

Nephrology Unit, A. Gemelli University Hospital Foundation IRCCS, Rome, Italy

"I do not accept the work because it is substantially unchanged from the points I previously examined".

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 13 January 2022

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Imed Helal

Diaverum AB Dialysis, Riyadh, Saudi Arabia

It was a pleasure to review this rare case report of silicosis and IgA nephropathy:

- Overall, this paper is based on rigorous academic standards and the content is technically accurate and sound.
- The abstract is concise and sufficient.
- The background of the case's history and progression described provide sufficient details.

- The supporting evidence in the discussion is reliable and sufficient.
- This paper is easy to read with sufficient detail to be useful for other practitioners.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical nephrology , dialysis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 December 2021

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Gisella Vischini

Nephrology Unit, A. Gemelli University Hospital Foundation IRCCS, Rome, Italy

The Authors describe a rare association between silicosis and IgA nephropathy. Based on previous studies already published in the literature, they summarise possible explanations in which hyperstimulation of low respiratory tract mucosa, aberrant IgA production and macrophages activation seem to play a crucial role.

The paper is grammatically well written; however, I think it is not enough from a scientific point of view.

I have expanded upon on my views below:

- Is the background of the case's history and progression described in sufficient detail?
Yes, the clinical history is well reported
- Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No, they are not. Previous published studies have done more tests on kidney biopsy in order to define the correct diagnosis and its pathogenesis (silica test on kidney biopsy, macrophage activation). Patient's follow up is three months: KDIGO suggest six months therapy before considering other therapies. I think the observation is too short.

- Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis, or treatment?

No, it is not. The Authors put together findings already published without adding any new elements useful for future understanding of disease processes, diagnosis, or treatment.

- Is the case presented with sufficient detail to be useful for other practitioners?

Yes, it is. The Author report a good practice management.

I have expressed my negative impression and therefore I did not approve the paper because, in my opinion, a description of a good clinical management not always is associated with a solid scientific process: the paper lacks about specific tests and or pathological findings that we need to have if we want to correlate two otherwise ordinary diagnosis among them. In that case is just a good description of a typical day work where clinicians look for support on papers already published on their clinical hypothesis.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Renal pathology, glomerulonephritis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 23 Dec 2021

Ikram Mami, La Rabta Hospital, Tunis, Tunisia

I want to thank you for agreeing to judge our work. In fact, the association of Ig A nephropathy and silicosis is exceptional and only a few reports were described in the literature. So, further investigations are needed to confirm such a hypothesis, but we think that our data should prompt clinicians to report similar cases to better understand the mechanisms underlying silica nephropathy.

Competing Interests: No competing interests were disclosed.

Reviewer Report 06 December 2021

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Imed Helal

Diaverum AB Dialysis, Riyadh, Saudi Arabia

This article presents an exceptional association of silicosis and IgA nephropathy excellent for discussion and teaching. Exposure to silica has been associated with tubulointerstitial disease, immune-mediated multisystem disease, chronic kidney disease and end-stage kidney disease. A rare association with glomerulonephritis has been reported.

I read this case report with interest and have a few comments and suggestions:

- There are several formatting and grammatical errors throughout the manuscript. Please correct.
- With the new published nomenclature in nephrology, please remove renal and write kidney instead.
- What is meant by the abbreviation NFS?
- The relationship between SILICOSIS and IgA nephropathy is not confirmed. Please provide more evidence.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical nephrology , dialysis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 22 Dec 2021

Ikram Mami, La Rabta Hospital, Tunis, Tunisia

- 1. There are several formatting and grammatical errors throughout the manuscript. Please correct.**

Grammatical errors were corrected in the new version.

- 2. With the new published nomenclature in nephrology, please remove renal and write kidney instead.**

The term "Renal" is replaced with the term "Kidney".

- 3. What is meant by the abbreviation NFS?**

NFS was translated to English in the new version.

- 4. The relationship between SILICOSIS and IgA nephropathy is not confirmed. Please provide more evidence.**

In our case, the diagnosis of silicosis was given by exposure to silica and the results of chest tomography. In fact, the diagnosis of silicosis needs occupational exposure and radiological features, with exclusion of other competing diagnoses.

Simultaneous kidney and pulmonary disease could lead to the hypothesis that IgA nephropathy might be associated with silica exposure.

In fact, IgA nephropathy seems frequent in patients with various pulmonary diseases, suggesting that an inflammatory process of the lungs may lead to IgA-mediated immune. In our case, the patient had also high C reactive protein level at 67 mg/l which suggests an inflammatory status.

Author of this article

Competing Interests: No competing interests were disclosed.

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