Case Report: Silicosis and IgA nephropathy, an exceptional association [version 1; peer review: awaiting peer review]

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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

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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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How to cite this article: Mami I, Hsinet J, Tlili S et al. Case Report: Silicosis and IgA nephropathy, an exceptional association [version 1; peer review: awaiting peer review] F1000Research 2021, 10:1146 https://doi.org/10.12688/f1000research.73525.1

First published: 11 Nov 2021, 10:1146 https://doi.org/10.12688/f1000research.73525.1
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. The most common silica nephropathies described to be related to silicosis are crescentic glomerulonephritis, proliferative glomerulonephritis and chronic interstitial nephritis. 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. 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 renal failure (serum creatinine 207 μmol/l, eGFR 26 ml/min) that was discovered during routine exams to follow-up his pernicious anemia, including creatinine, NFS and haemoglobin. 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 of supervising concreting, masonry, foundations, walls and floors covering as well as painting and finishing. During his professional career, he was 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 renal failure with a creatinine level at 207 μmol/l (normal range >60 μmol/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 11g/dl (anemia shown by level <13g/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 renal 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 sclerosed. 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 chronic crystalline silica exposure, characteristic radiologic findings and clinical signs, the diagnosis of silicosis was given.

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. Renal 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.

Discussion
Occupational silica exposure causes not only lung damages, but also involves many other organs. 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.\textsuperscript{8} Little is known about mechanisms, but it has been reported that silica dust triggers autoimmune phenomena.\textsuperscript{2} Moreover, several authors have reported the association of silicosis with kidney lesions as an occupational disease.\textsuperscript{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 renal disease.\textsuperscript{1} The most common silica nephropathy described in the literature were crescentic glomerulonephritis, proliferative glomerulonephritis and chronic interstitial nephritis.\textsuperscript{3} IgA nephropathy had been rarely reported even though it is the most common type of glomerulonephritis worldwide.\textsuperscript{10} Only a few similar cases were described in the literature.\textsuperscript{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 process.\textsuperscript{11} According to the medical history of the association of lung and kidney disease, Endo \textit{et al} had reported that not only upper tract, but also the lung or lower respiratory tract is a mucosal site protected by IgA.\textsuperscript{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.\textsuperscript{12} This process mimics the immunopathologic features of IgA nephropathy and may confirm that this glomerulonephritis may occur secondary to silicosis. Beshir \textit{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).\textsuperscript{13} 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.\textsuperscript{3,14}

\textbf{Figure 1. Renal biopsy specimen diagnosed with Ig A nephropathy.} A,B: Light microscopic, hematoxylin and eosin- stained (×200), segmental mesangial hypercellularity. C: Light microscopic, Periodic Acid Schiff (× 200), flocculo-capsular synechiae. D: Immunofluorescence microscopy (×200), Mesangial IgA deposits.
The real mechanism and pathophysiology are still not fully elucidated and needs 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. However,
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Age (Y)/sex</th>
<th>Profession</th>
<th>ABP (mmHg)</th>
<th>Hu</th>
<th>Pr (g/24h)</th>
<th>Serum creatinine</th>
<th>Renal biopsy findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonnin A et al. 1987(^2)</td>
<td>69/M</td>
<td>Miner</td>
<td>200/100</td>
<td>Yes</td>
<td>3</td>
<td>106 μmol/l</td>
<td>IgA mesangial nephropathy associated to crescents</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>50/M</td>
<td>Ceramic enamelling</td>
<td>150/90</td>
<td>Yes</td>
<td>1.1</td>
<td>165 μmol/l</td>
<td></td>
<td>PE</td>
</tr>
<tr>
<td></td>
<td>67/M</td>
<td>Miner</td>
<td>190/100</td>
<td>Yes</td>
<td>3</td>
<td>212 μmol/l</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>A R Khan et al 1999(^4)</td>
<td>45/M</td>
<td>Tunnel construction worker</td>
<td>160/100</td>
<td>Yes</td>
<td>4.2</td>
<td>1.2 mg/dl</td>
<td>IgA nephropathy with deposited interstitial nephritis</td>
<td>-</td>
</tr>
<tr>
<td>Fujii Y et al. 2001(^3)</td>
<td>51/M</td>
<td>Building wrecker</td>
<td>-</td>
<td>Yes</td>
<td>0.294</td>
<td>-</td>
<td>Mesangial proliferation with IgA deposition</td>
<td></td>
</tr>
<tr>
<td>Ricco M et al. 2016(^6)</td>
<td>68/M</td>
<td>Sandstone cave miner</td>
<td></td>
<td>Yes</td>
<td>2.8</td>
<td>2 mg/dl</td>
<td>Glomerular sclerosis with IgA deposition and tubular atrophy</td>
<td>Immune suppressing therapy</td>
</tr>
<tr>
<td>Chen F-F et al. 2019(^3)</td>
<td>43/M</td>
<td>Coal miner</td>
<td>130/80</td>
<td>Yes</td>
<td>3.7</td>
<td>2.51 mg/dl</td>
<td>Focal proliferative IgA nephropathy and acute tubulo-interstitial nephritis</td>
<td>Corticosteroids + ACEI</td>
</tr>
<tr>
<td>Our case</td>
<td>57/M</td>
<td>Mason</td>
<td>150/90</td>
<td>Yes</td>
<td>1.5</td>
<td>207 μmol/l</td>
<td>Mesangial proliferation with IgA deposition associated to tubular atrophy and interstitial fibrosis</td>
<td>ACEI</td>
</tr>
</tbody>
</table>

M: Male; Y: Year; ABP: Arterial Blood Pressure; Pr: Proteinuria; Hu: Hematuria; PE: Plasma exchange; ACEI: Angiotensin-Converting Enzyme Inhibitors.
vasculitis and immune-mediated disease required steroids and cytotoxic agents in addition to reducing exposure to silica crystalline dust.\textsuperscript{9}

In our case, steroids or immunosuppressant agents were not required because of the absence of active lesions on renal biopsy. Thus, only antihypertensive treatment with a nephroprotective effect was initiated in association with a withdrawal from the occupational exposure. Moreover, chronic lesions, such as tubular atrophy and interstitial fibrosis might explain the degree of renal 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,\textsuperscript{1} while others had reported that renal disease or progression is associated with a worsening lung involvement.\textsuperscript{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.

References

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